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Multi-faceted Commercially Sourced Pd-Supported Reduction: A View from Practical Experience

Abstract

Aim. To share our experience when working with the Pd-catalyzed hydrogenation and discuss reactions occurred contrary to our expectations, as well as express our vision of the causes for such an unusual reactivity.

Results and discussion. Catalysis is a key technology and among the central themes of both petrochemical and fine chemical industries. Although extremely useful and reliable, it can sometimes astonish researchers. The paper discusses 17 intriguing cases of the catalytic hydrogenation and hydrogenolysis reactions from our practice in the High-pressure Synthesis Laboratory (Enamine Ltd.). All examples presented are characterized by peculiar performance of commercially sourced heterogeneous palladium-containing catalysts (Pd/C or $Pd(OH)_2$). Thus, some cases were characterized by reduced activity of the catalyst (or even its complete loss), meaning that reaction conditions found before to be suitable for reduction appeared to be "broken", and we had to search for a new, often harsher reaction setup. Curiously, it is a matter of classical Pd-catalyzed hydrogenations of N^+–O^- and C=C fragments. Apparently, these results indicate the heterogeneity of commercially available catalysts and are related to their fine internal structure, in particular the surface morphology. Another interesting issue the article deals with is chemoselectivity of the catalytic hydrogenation. Sometimes some reactions led to astonishing results going across theoretical views and expectations. Saturation of benzene rings instead of (or accompanying) debenzylation, breaking of the common order of hydrogenation for compounds containing several aromatic parts with different resonance energies, irreproducible experiment, obtaining of different products under the same conditions, uncommon results of Pd-catalyzed reactions is the list of interesting results, which we observed and discussed in the article. Analyzing the information available in the literature and considering all the results gathered we tend to believe that the presence of impurities of noble metals (Rh, Ru, Pt) in the catalysts used to be a possible reason for these strange findings. The study supports the general idea that commercial palladium catalysts differ in efficiency, resulting in significant differences in selectivity, reaction time, and yields. Elucidating the regularities behind such empirical results is undoubtedly an interesting area of research in the field of catalysis.

Experimental part. All starting compounds exposed to hydrogenation were synthesized in Enamine Ltd. and had purity of not less than 95 %. The palladium-containing catalysts used in the experiment were purchased from 6 commercial sources within 2011 – 2022. The structure and purity of the compounds synthesized were characterized by ^{1}H NMR spectroscopy, liquid chromatography coupled with the mass spectrometry method, elemental analysis. Chromatographic experiments revealed the purity of all compounds obtained being not less than 95 %.

Conclusions. In the paper we have summarized our experience with the Pd-catalyzed hydrogenation and presented cases of unusual reactivity or unexpected outcomes of the reactions encountered in our practice. In general, complications we faced were of three types: (1) irreproducibility of the procedures most likely as the result of a changeable activity of the catalysts; (2) chemoselectivity issues when two or multireducible functional groups were present in the substrate; (3) undesirable Pd-catalyzed defunctionalization reactions. In turn, these complications led to increase in production costs, loss of time and resources. Therefore, because of this variability in the efficiency of Pd catalysts, far more efforts are required to find out the key differences between commercial sources of Pd catalysts, as well as to create protocols clearly defining the catalytic activity of each batch of the catalyst allowing to identify high-quality catalysts immediately prior to the use without wasting precious time and synthetic materials.

Keywords: catalysis; hydrogenation; heterocyclic compounds; palladium; selectivity; competing reactions

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Багатогранне відновлення, каталізоване комерційно доступним паладієм: погляд на реакцію із практичного досвіду

Анотація

Мета. Метою статті було поділитися нашим досвідом роботи з Pd-каталізованим гідруванням і обговорити реакції, що відбувалися всупереч нашим очікуванням, а також висловити своє бачення причин такої незвичайної реакційної здатності.

Результати та їх обговорення. Каталіз є ключовою технологією та однією з центральних тем як нафтохімічної, так і тонкої хімічної промисловості. Хоча він є надзвичайно корисним і надійним підходом, іноді він може дивувати дослідників. У пропонованій статті розглянуто 17 цікавих випадків реакції каталітичного гідрування з нашої практики в Лабораторії синтезів під високим тиском (НВП «Єнамін»). Усі наведені приклади характеризуються своєрідною поведінкою комерційно доступних гетерогенних паладієвмісних каталізаторів (Pd/C або $Pd(OH)_2$). Так, деякі випадки характеризувалися зниженою активністю каталізатора (або навіть повною її втратою). Іншими словами, умови реакції, які ми раніше вважали придатними для відновлення, виявилися «зламаними», і нам довелося шукати нові, часто жорсткіші умови для проведення реакції. Цікаво, що мова йде про класичне Pd-каталізоване гідрування N^+–O^- і C=C фрагментів. Певно, ці результати свідчать про різнорідність комерційно доступних каталізаторів і пов'язані з їхньою тонкою внутрішньою структурою, зокрема морфологією поверхні. Іншим цікавим питанням, висвітленим у статті, є хемоселективність каталітичного гідрування. Так, іноді реакція призводила до вражаючих результатів, що суперечили теоретичним поглядам і очікуванням. Насичення бензольних кілець замість дебензилювання (або разом із ним), порушення загального порядку гідрування для сполук, які містять кілька ароматичних частин з різною енергією резонансу, невідтворюваний експеримент, отримання різних продуктів за використання однакових умов, нетипові результати реакцій, каталізованих Pd, – це список тих результатів, які ми спостерігали та обговорюємо в статті. Аналізуючи наявну в літературі інформацію та враховуючи всі зібрані результати, ми схильні вважати причиною цих дивних знахідок наявність у використаних каталізаторах домішок благородних металів (Rh, Ru, Pt). Дослідження несе загальну ідею про те, що комерційні паладієві каталізатори відрізняються за ефективністю, що призводить до значних відмінностей у селективності, часі реакції та виході. З'ясування закономірностей, що стоять за такими емпіричними результатами, безсумнівно, є важливим напрямом досліджень у царині каталізу.

Експериментальна частина. Усі вихідні сполуки, піддавані гідруванню, було синтезовано в ТОВ «Єнамін». Вони мали чистоту не менше 95 %. Використовувані в експерименті каталізатори з паладієм було закуплено у 6 комерційних джерел упродовж 2011–2022 років. Структуру та чистоту синтезованих сполук схарактеризовано методами ^{1}H ЯМР-спектроскопії, рідинної хроматографії в поєднанні з мас-спектрометричним методом, елементного аналізу. Хроматографічні дослідження засвідчили, що чистота всіх одержаних сполук становить не менше 95 %.

Висновки. У статті узагальнено досвід роботи з Pd-каталізованим гідруванням і розглянуто випадки незвичайної реактивності або неочікуваних результатів реакцій, які зустрічалися в нашій практиці. Загалом ускладнення, з якими ми зіткнулися, були трьох типів: (1) невідтворюваність процедур, найпевніше, у результаті варіативної активності каталізаторів; (2) проблеми хемоселективності, у випадку присутності в субстраті кількох функціональних груп, здатних до відновлення; (3) небажані реакції дефункціоналізації, каталізовані Pd. Своєю чергою ці ускладнення призвели до збільшення витрат на виробництво, втрати часу та ресурсів. Саме через таку варіабельність ефективності паладієвих каталізаторів потрібно значно більше зусиль, щоб з'ясувати ключові відмінності між комерційними джерелами Pd-каталізаторів, а також створити протоколи, які чітко визначають каталітичну активність кожної партії каталізатора, що дозволяє ідентифікувати високоактивні Pd-каталізатори безпосередньо перед використанням і не втрачати дорогоцінний час та синтетичні матеріали.

Ключові слова: каталіз; гідрування; гетероциклічні сполуки; паладій; селективність; конкурентні процеси

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Introduction

Catalysis is the most powerful method of controlling and directing chemical reactions, and it is widely used as a viable avenue for preparing compounds, which are hard to access by common catalyst-less approaches. Thus, as of 2002, more than 70% of industrial processes were catalytic, and, indeed, the value has only increased over the years [1]. Moreover, it was estimated that production of more than 90% of all chemical products requires at least one catalytic step [2].

Undoubtedly, the catalytic hydrogenation (and hydrogenolysis as well) has an enormous impact on and constitutes a key technology in petrochemical, fine chemical, pharmaceutical and environmental industries. The statement is eloquently supported by two Nobel prizes awarded to *Paul Sabatier* (1912, "for his method of hydrogenating organic compounds in the presence of finely disintegrated metals…"), and *William S. Knowles* and *Ryoji Noyori* (2001, "for their work on chirally catalyzed hydrogenation reactions") [3–5]. A large-scale conversion of benzene to cyclohexane and the production of *L*-DOPA, a drug used to treat Alzheimer's disease, are instructive examples of the reaction. Over more than 100 years numerous catalysts, both homogeneous and heterogeneous, have been adjusted to the hydrogenation though usually most of them contain a noble-metal core (Au [6], Pt [7], Rh [8], Ru [9], Ir [10], or Pd [11]) as an active site for the reaction. As indicated by a patent landscape analysis, the process of developing new catalysts has accelerated over the last 25 years [12]. Thus, starting from the middle of 1990s more than 1000 patents have appeared in the scientific field as compared to only about 500 for the previous 70 years (from 1925 to 1995). It is noteworthy, that the amount of patents protecting heterogeneous catalysts increases twice as fast as homogeneous ones. The fact accounts for advantages of the heterogeneous nature of former ones as they are recoverable and reusable, hence showing excellent economy properties, as well as suitable for flow chemistry processes. Therefore, it is no wonder that the catalytic hydrogenation occupies about 10–20% of the reactions used to produce chemicals [13].

In this regard, palladium is probably the most widely used metal component in the heterogeneous catalytic hydrogenation with carbon-supported palladium being a well-established heterogeneous catalyst. Thus, the largest number of patent families (1753 for the period of 2011–2015) was identified for palladium. Moreover, this amount is unceasingly growing [14]. About 75% of modern industrial hydrogenation processes are carried out in the presence of a Pd/C catalyst [15] and, no wonder, it is widely applied to the synthesis of various chemicals of industrial and academic interest [16, 17].

Despite the undoubted progress in developing catalytic systems in general and Pd-containing ones in particular, their preparation still involves complex procedures that make it difficult to obtain a reproducible catalytic body [18]. Thus, the way a heterogeneous catalyst is manufactured crucially determines its characteristics, e.g. fine structure, surface characteristics, catalytic activity, selectivity and lifetime. All of the above results in significant variability in the efficiency of commercial sources of palladium on carbon. Such a situation becomes a striking problem as the determination of catalysts' features needed for their effective application is a tedious, time- and resource-consuming task and obviously cannot be accomplished for each batch of the catalyst [1, 19]. For this reason, a few attempts have been made to standardize and determine the qualities of carbon-supported palladium aiming to provide an effective tool for the prediction of the catalyst's efficiency prior to its use and to save valuable synthetic material and time [20–22]. In spite of valuable findings, these studies did not completely eliminate the problem as they inherently contained limitations. Among others, they include awkward procedures and difficult-to-obtain standard substrates. Moreover, the methods developed cannot detect the selectivity of Pd catalysts with respect to structural variations of the substrate. As the result, palladium/carbon catalysts remain a "black box" for synthetic chemists. Nowadays, familiarizing such catalysts is essentially a trial-and-error process requiring extensive testing in order to identify efficient catalysts, and find out suitable reaction parameters of short reaction times and high isolated yields.

Hydrogenation and hydrogenolysis are principal processes in the production cycle of fine chemicals existing in our company (High-pressure Synthesis Laboratory of Enamine Ltd.). Every day we deal with the hydrogenation of numerous substrates, bur not always successfully. From time to time we obtain unexpected results varying from '*conditions found previously do not work*' to '*how is it possible for the compound to be obtained here?*'.

Often, we get in such a tight spot when switching from one catalysts' supplier to another though we could not deny a contribution of the substrate peculiarities to the unwanted outcome.

In this article we would like to share our enormous experience of working with the Pd-catalyzed hydrogenation, as well as in some cases express our vision of the reasons of such an odd reactivity. Nevertheless, this work is not intended to find out and discuss the fundamentals of hydrogenation reactions.

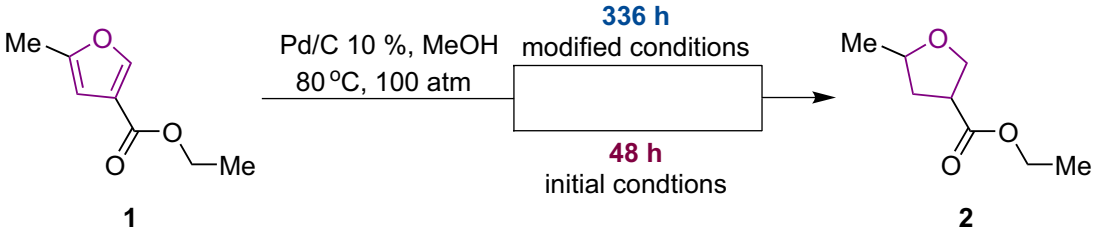
■ Results and discussion

The palladium-catalyzed hydrogenation can be performed with nearly all types of unsaturated bonds. In addition, even single C-O and C-N bonds can be broken under the Pd catalysis. The common range of substrates suitable for the Pd catalysis covers the following 3 groups of organic compounds: (1) unsaturated hydrocarbons and (hetero)arenes; (2) carbonyl-containing compounds; (3) classes with nitrogen-containing multiple bonds. In most of the cases, Pd is either the most satisfactory or one of the most satisfactory catalysts. However, one should emphasize here again that it is a matter of relative rates, the structure of a Pd catalyst, reaction conditions, and so on. In this regard, conditions that we found before to be suitable for reduction (referred to as '*initial conditions*' throughout the paper) sometimes appeared to be "broken" so that we had to search for new, often harsher conditions ('*modified conditions*').

The first example of conditions no longer working is given in Scheme 1. It illustrates the complete reduction of a furan moiety to obtain tetrahydrofuran derivative **2**. Usually, similar reactions proceed readily with a Pd/C catalyst under mild conditions [23, 24]. As there is no data on reducing compound **1** we have found out appropriate conditions enabling such a transformation and including 48-hour protocol. Repeating the reaction later we were stunned by the time required for 100% conversion of the starting furan (monitoring by ^{1}H NMR) being 7 times more than it was determined before. The change is definitely caused by the activity of the catalyst, which, in turn, is related to its fine internal structure, most likely another surface morphology. The observation brings us back to the question of the reliability and reproducibility of the published procedures. One should note that compound **2** was unknown before. Considering the fact that tetrahydrofuran-3-carboxylates have been found to possess valuable biological properties [25, 26] the approach may provide access to new potent agents.

Nitrogen-containing multiple bonds are another well-established substrate for the Pd-catalyzed reduction [27]. Thus, the hydrogenation of compound **3** was already known [28] (Raney Ni, MeOH, 40°C, 40 atm, 3 h) and was formerly used as a step in the synthesis of potential inotropic agents [29, 30]. Both N-functionalities underwent reduction simultaneously resulting in 4-amino-3-methoxypyridine (**5**). Performing the reaction in the presence of 10% Pd/C we obtained the same result (Scheme 2). However, this interaction was able to surprise us the next time when intermediate N-oxide **4** was observed under the same conditions. In open sources, we were unable to find a similar transformation occurring with loss of nitro and retaining N-oxide moiety, apparently due to their close tendency to reduction. To overcome the problem of the undefined catalyst activity, we tested various conditions and found that $Pd(OH)_2$ gave the desired derivative **5**, and, importantly, the reaction was reproducible. Elucidating the regularities underlying the partial recovery is undoubtedly an interesting area of research in the field of catalysis.

Scheme 3 depicts another unexpected case representing the absence of the catalytic activity of a Pd/C catalyst. Application of the 'initial conditions' led to recovering the starting material. This may sound weird as palladium displays an excellent catalytic performance in the hydrogenation of alkene compounds, even conjugated and partially aromatic, and serves as a classical



Scheme 1. The furan ring reduction – the reduced catalyst activity

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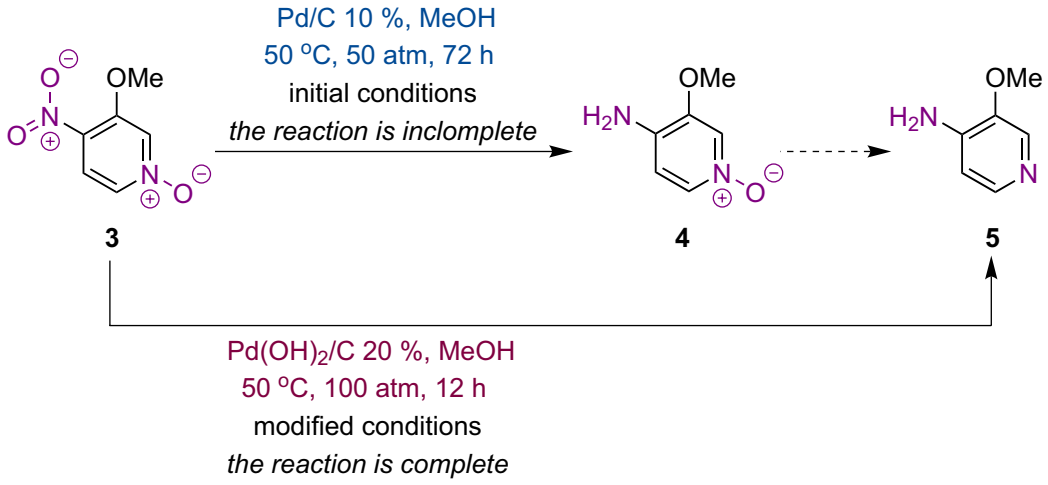
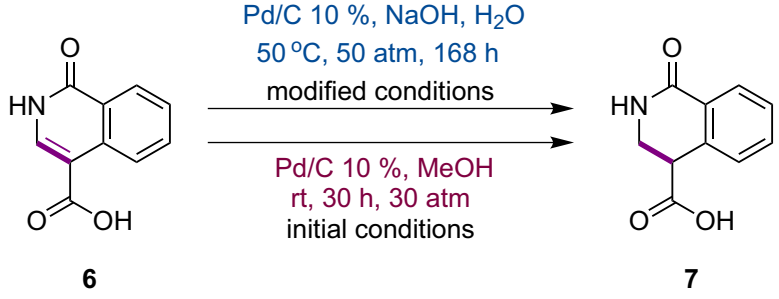


Scheme 2. A partial reduction of the nitropyridine N-oxide

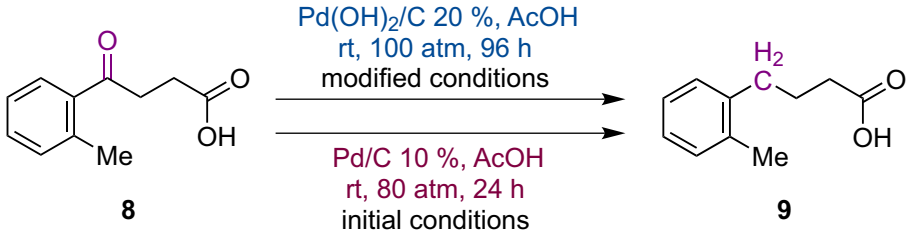
catalyst in such interactions [22, 31]. Moreover, the hydrogenation of the methyl ester required 4 hours to be accomplished under similar conditions [32]. Apparently, the problem was the heterogeneity of the catalyst and the presence of microparticles instead of nanoparticles. We managed to fix the problem and obtained acid **7** applying harsher conditions in an amount of up to 20 g in a run. It is interesting to note that the reaction may have an additional value as the N-methyl derivative of isoquinolone **7** showed high efficacy in inhibiting *E. coli* DNA gyrase [33].

The reductive deoxygenation of ketones allowing the substitution of the C=O group with a CH_2 fragment has attracted great attention given its numerous applications in the synthesis of fine chemicals and biofuel production [34]. Since classical methods for the deoxygenation of carbonyl compounds (Barton–McCombie, Clemmensen, Wolff–Kishner methodologies) are generally associated with harsh reaction conditions, the use of stoichiometric amounts of toxic reagents, and the poor functional-group tolerance [35], a number of advanced catalytic protocols for the deoxygenation of carbonyls employing 'green' molecular hydrogen [36–39] have been reported. Some papers describe practical and mild methods for the deoxygenation utilizing supported palladium catalysts [40–42]. We also contributed to the field as we developed a method for the reductive deoxygenation of ketoacid **8** into tolylbutyric acid **9** promoted by 10% Pd/C catalyst (Scheme 4). As with the previous reactions this protocol turned out to be unreliable. Thus, we worked out a more credible and efficient large-scale procedure employing the $Pd(OH)_2/C$ catalytic system. The transformation discussed is described in only one work and based on the 'unfriendly' Huang-Minlon-Wolff-Kishner procedure, which provides compound **9** with lower yields [43]. The fact is important as acid **9** has shown to be a useful agent in treating conditions associated with ER-stress, including diabetes, hypercholesterolemia, atherosclerosis, etc. [44].

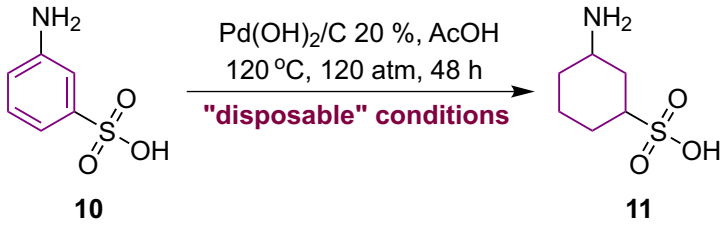
The next reaction appeared to be a tough nut to crack for the heterogeneous palladium-catalyzed reduction is the hydrogenation of metanilic acid (**10**), which succumbed to our efforts only once giving cyclohexanesulfonic acid **11** in a low yield. Our multiple later attempts resulted in nothing as the only isolated material was the starting metanilic acid with no signs of its conversion into the target compound according to the LC-MS analysis. Presumably, an answer to the riddle is hidden in the fact that Pd is less active in the saturation of aromatics than other



Scheme 3. The search for suitable conditions – conversion of 'alkene' into 'alkane'



Scheme 4. The search for suitable conditions – reductive deoxygenation



Scheme 5. A single reduction of benzene into cyclohexane

precious metals (Pt, Ru, Rh). Reduction of compound **10** was reported to be successful in good yields under the hydrogenation catalyzed by Rh supported by Al_2O_3 in acidic conditions [45]. Owing to this fact one can suspect that our 'lucky' catalyst contained an impurity of rhodium, which was a real catalyst of the reaction. Thereby, one should keep in mind that catalysts can vary in both a fine structure and purity. If the former mainly affects the activity of the catalyst, the other may turn the reaction in an unexpected direction.

Protecting groups constitute an essential instrument in the synthesis of both natural and artificial chemicals [46]. Synthetic avenues towards complex, often natural, compounds are tricky, requiring multistep protecting group manipulations [47, 48]. Additionally, only a small amount of the starting material can be available, which creates the problem of high yields and selectivity of the deprotection step [49, 50]. In this regard, the palladium-catalyzed hydrogenolysis is one of the most common problems we face. In general, it involves the removal of benzyl ether and N-benzyl protecting groups in order to release OH- and NH-functionalities. Usually everything goes smoothly, and such a deprotection sometimes becomes a serious obstacle on the way to the product, as also reported earlier [51].

Schemes 6 and 7 represent our struggle for *O*- (azetidinecarboxylic acid **12**) and *N*-debenzylation (oxazepan **14** and pyrrolidine **16**), respectively. Once deprotected easily under relatively mild ordinary conditions (10% Pd/C, MeOH, 50°C), the reactions refused to repeat and form the target compounds **13**, **15** and **17** in the presence of the abovementioned catalytic system though some papers described the use of Pd/C in similar preparation of heterocycles **15** and **17** [52, 53]. As in the previous cases, this is associated with a decrease in the activity of catalysts due to an increase in the particle size and changes in the surface morphology.

However, we have found that the use of palladium hydroxide is a more reliable and reproducible approach, as we noted earlier. The results obtained are somewhat consistent with those reported by *Yong Li et al.* [54]. The paper indicates the absence of the catalytic activity in some cases for Pd/C and $Pd(OH)_2/C$ used separately, while their combination serves as an excellent catalyst for the removal of *O*- and *N*-benzyl fragments. Although there is currently no mechanistic basis for this observation, we believe that the formation of a $Pd/Pd(OH)_2/C$ mixture during the hydrogenation may contribute to the successful outcome of reactions. Finally, we would like to note that neither the hydrogenolysis of the azetidine derivative **12** nor product **13** is covered in the literature although similar azetidine carboxylic acids have been considered as conformationally constrained GABA or β-alanine analogs and, therefore, have been evaluated for their potency as GABA-uptake inhibitors [55]. Our results expand possibilities for the research, as well as provide a new interesting experimental material for studies in the field of medical chemistry.

While foregoing results mainly concerned issues of the catalyst activity loss and searching for new suitable conditions, the next part of the work is going to highlight various selectivity aspects of the Pd-catalyzed hydrogenation and hydrogenolysis.

Sometimes reactions lead to astonishing results going across theoretical views and expectations.

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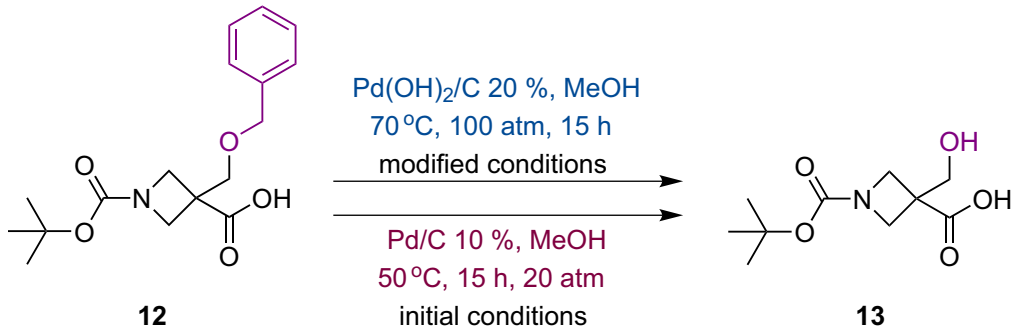
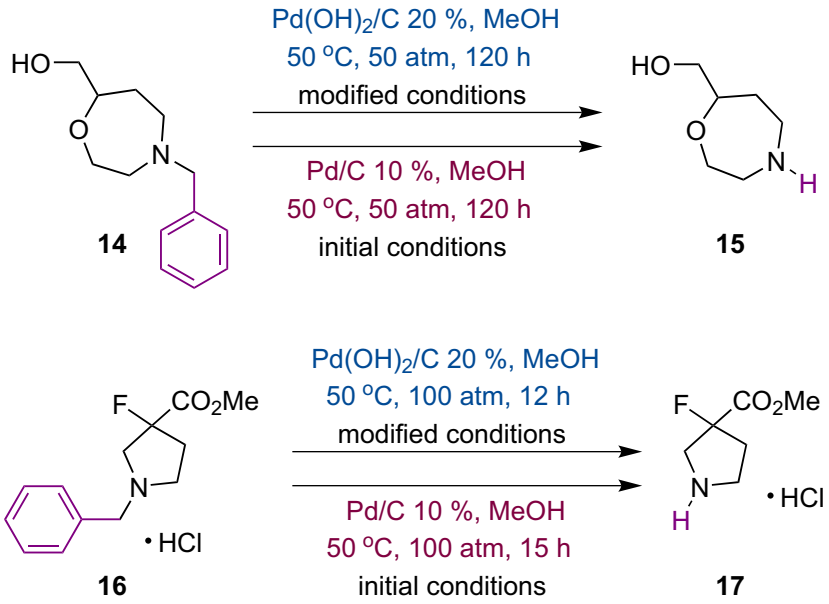


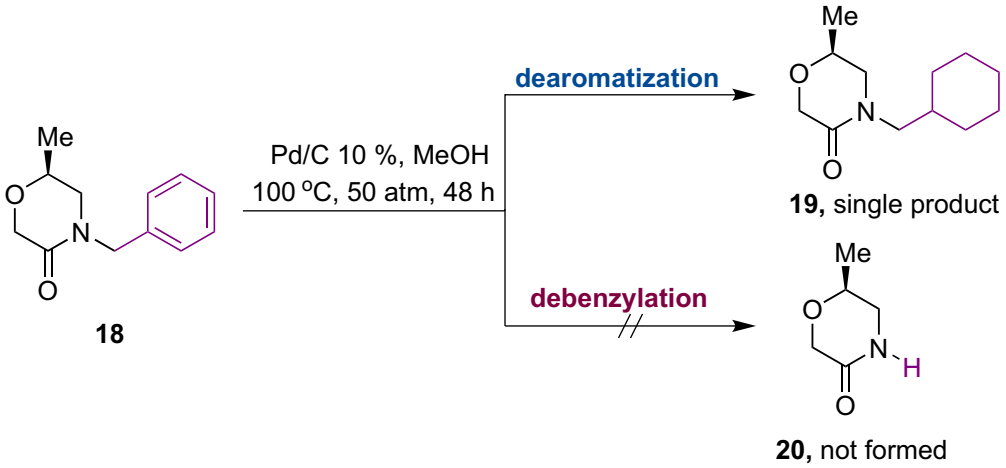
Scheme 6. The search for suitable conditions – *O*-debenzylation



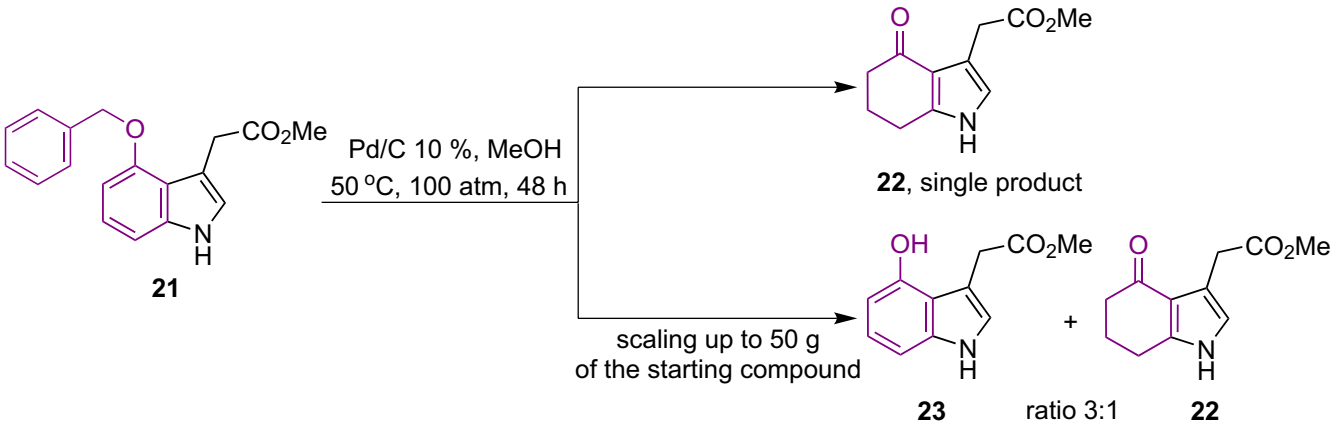
Scheme 7. The search for suitable conditions – *N*-debenzylation

In continuation of the deprotection question Schemes 8 and 9 show a kind of shocking outcomes, which we observed during the *N*- and *O*-debenzylation of derivatives of morpholine **18** and indole **21**, respectively. In the first case, we failed to obtain the target product **20**. Instead, the only recovered compound was cyclohexyl derivative **19**. The latter is obviously formed by the saturation of the benzene ring being the dominant direction of the reaction since we could not detect any traces of the desired morpholinone. The subsequent variations of the reaction conditions did not give compound **19** as well. The situation seems to be strange as palladium is often preferred over other noble-metal catalysts due to its lower propensity to cause the saturation of aromatics [56]. This unexpected dearomatization of the benzyl moiety was previously observed and reported on examples of benzyl and naphthylmethyl ethers [57, 58]. The authors suggested that the process may be attributed to the self-inhibition of the Pd/C catalyst by intramolecular nitrogen-containing basic centers. Although the structural features of substrate **18** may affect the direction of the interaction, we think that another reasonable explanation would be the presence of other noble metal (Rh, Pt) impurities in the catalyst used.

As indicated by Scheme 9, our initial experiments on the deprotection of benzyloxy derivative **21** resulted in the isolation of ketone **22** as a single product. In this case, the hydrogenolysis was not a terminated step as it was followed by the partial hydrogenation of the benzene moiety. Curiously, despite the lower resonance energy of the separated pyrrole compared to benzene, the former was not hydrogenated during the reaction. Although the data for the debenzylation of exactly compound **21** is not available, there are plenty of other examples of the hydrogenolysis reaction employing 4-benzyloxyindoles (about 340 according to the Reaxys® database). Interestingly, all the reactions give exclusively 4-hydroxyindoles with no any allusion to ketones similar to **22**. Thus, being surprised but interested in getting additional portions of compound **22**, we increased the reaction scale to 50 g. Another surprise awaited us. The recovered material was a 3 to 1 mixture of phenol **23** and ketone **22**



Scheme 8. An unexpected dearomatization of benzene



Scheme 9. An unexpected hydrogenation of the benzene moiety of indole

according to LC-MS data. The result allows us to suggest that a stepwise format of the reaction includes a primary debenzylation step followed by the benzene moiety reduction. We also tend to believe that the presence of precious metal (Rh, Pt) impurities is the cause for this behavior. Inspired by the latest experiment, we are currently making constant attempts to solve the problem and find suitable as well as reproducible reaction conditions that provide exclusively any of products **22** and **23**.

In contrast to Scheme 9, the hydrogenation of benzofuran **24** proceeded the way it was expected with the reduction of the 'less aromatic' furan moiety of the molecule and gave dihydro derivative **25** (Scheme 10). The only difficulty that we encountered was the irreproducibility of conditions previously found to be suitable. Subsequently, we managed to find satisfactory ones giving compound **25** with any batch of the catalyst.

Minor structural variations of benzofuran **24**, namely the substitution of benzene moiety with the pyridine core, drastically changed the direction of the hydrogenation reaction promoted by 10% Pd/C (Scheme 11). Thus, the reduction of furo[3,2-*c*]pyridine-2-carboxylic acid (**26**) did not give the expected 2,3-dihydro product **30**. Moreover, the selectivity observed for benzofuran **24** was lost. As evidenced results of LC-MS and ^{1}H NMR investigations of the isolated mixture, the reduction occurred stepwise with the pyridine ring reduced first (compound **27**) followed by the formation of perhydro derivative **28**. Even more interesting, numerous studies report a reduction exclusively for the furan moiety for variously substituted furo[3,2-*c*]pyridines. The information about the complete reduction of furo[3,2-*c*]pyridines is not available as well. We did not succeed in elaborating more selective conditions using Pd-containing catalysts. So far, selective reduction of compound **26** remains an open question definitely deserving attention as some 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridines and octahydrofuro[3,2-*c*]pyridines have proven to be valuable pharmaceutical components [59, 60].

Another interesting example for discussing the chemoselectivity of the catalytic hydrogenation is given in Scheme 12. Compound **31** comprises 2 aromatic fragments of benzene and pyridine

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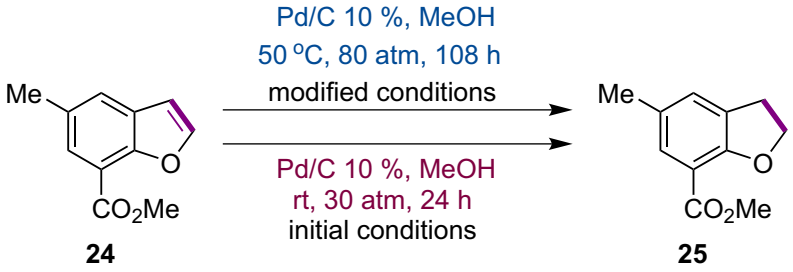
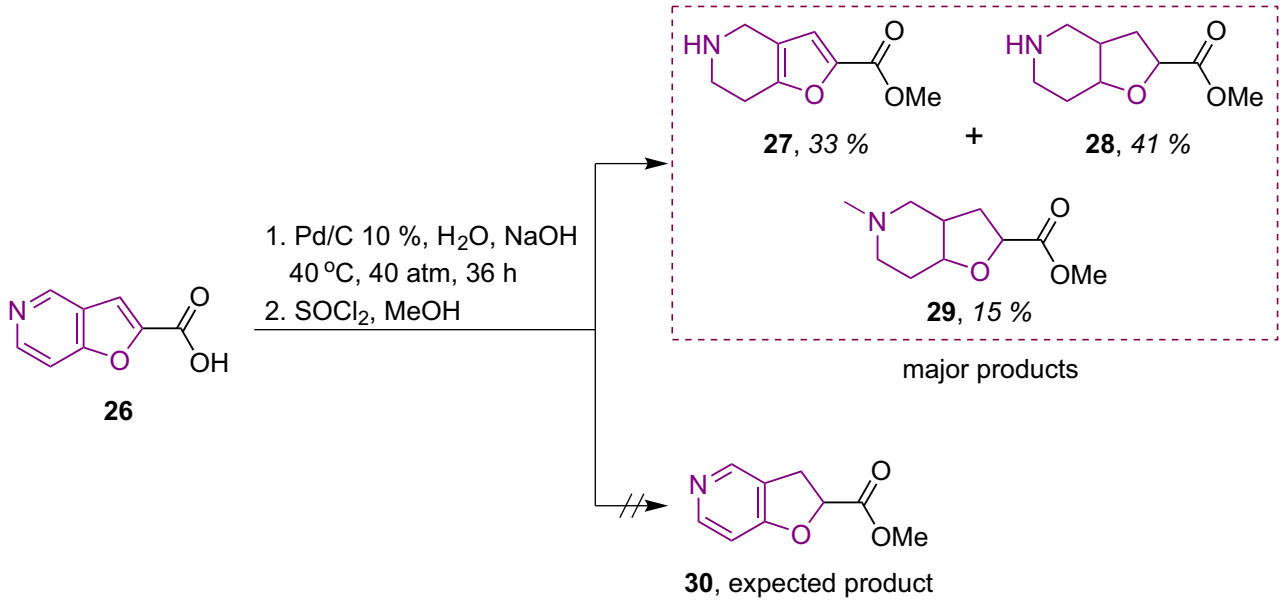
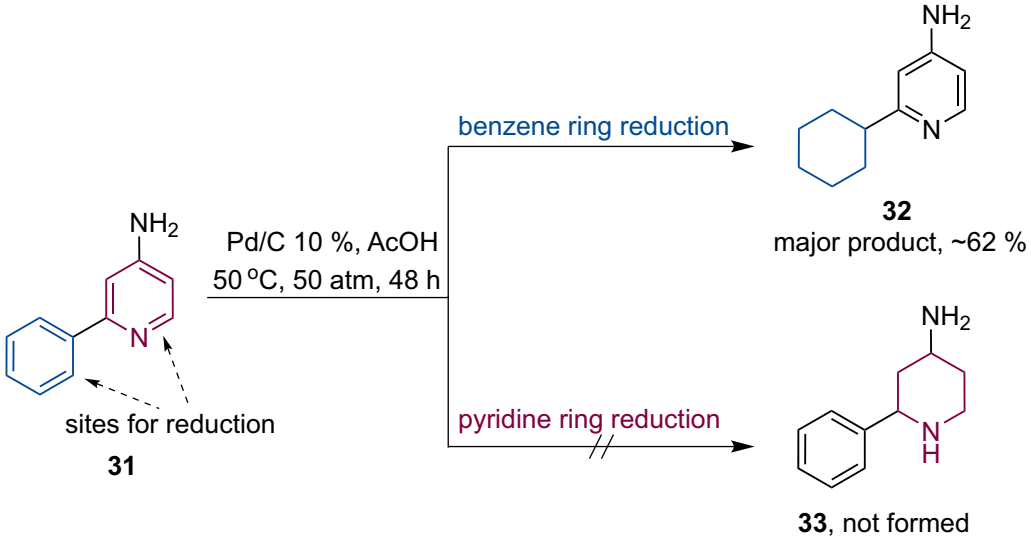


Scheme 10. The search for suitable conditions – benzofuran reduction

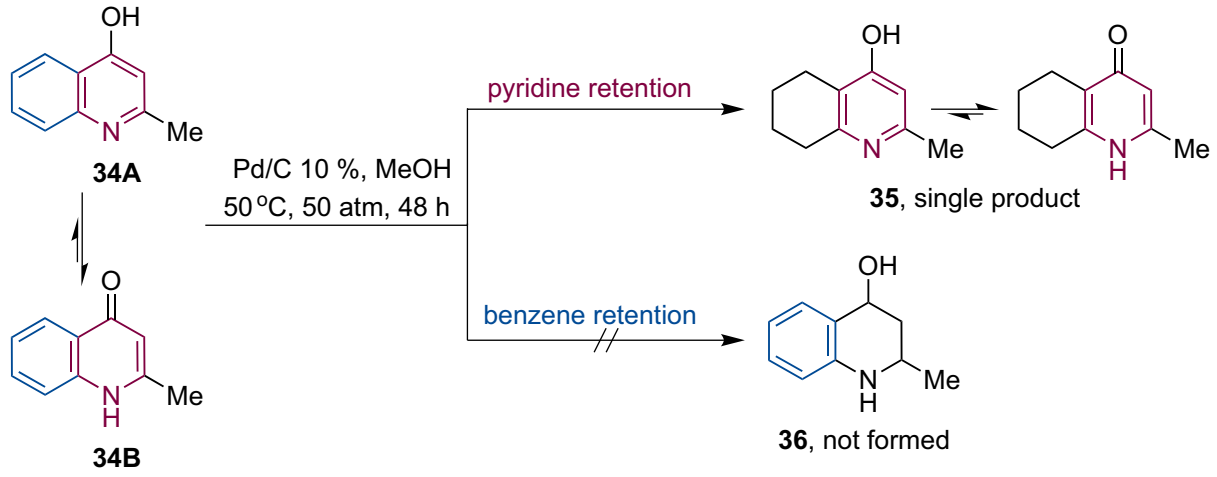


Scheme 11. Competing pathways in reduction of furo[3,2-*c*]pyridine

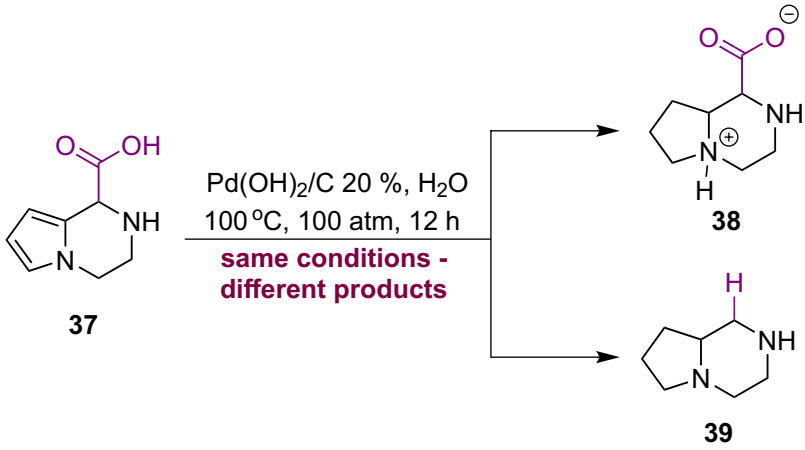


Scheme 12. Competing pathways in reduction of 2-phenylpyridine

joined by a σ-bond and both are potential sites for the catalytic reduction. Numerous studies examining the Pd-catalyzed reduction of 2-phenylpyridines have shown that the hydrogenation of the pyridine ring is best performed under acidic conditions, and phenyl rings are usually not reduced in significant amounts during the process [14, 61, 62]. We were able to find only three examples reporting the non-selective reduction of both pyridine and benzene fragments of the 2-phenylpyridine platform. Interestingly, all of these studies work with other precious metals – Ru(0) [63], Rh(II) [64], Pt(0) [65]. Moreover, the application of Ru(0) allowed the neutral benzene



Scheme 13. Competing pathways in reduction of quinoline



Scheme 14. An unexpected reductive decarboxylation

ring to be selectively reduced instead of the more electron-deficient pyridine ring, implying a possible directed hydrogenation by a Ru(0) catalyst. Interestingly, in our experiments on the Pd/C promoted hydrogenation of compound **31**, a dominant compound in the isolated mixture was also 2-cyclohexylpyridine **32** and not the product of the reverse chemoselectivity – piperidine **33** (according to ^{1}H NMR and LC-MS data). Again, we have the ground to suspect contamination of the Pd-catalyst with more active noble metals leading to controversial results.

The last substrate, we want to discuss, with two alternative centers for hydrogen attack is 4-hydroxy-2-methylquinoline (**34**). Its structure implies the formation of products **35** and **36** retaining pyridine and benzene moieties, respectively. Taking into account theoretical views of the aromaticity of benzene and pyridine one may predict that the pyridine moiety is more likely reduced as a less thermodynamically stable one. Moreover, compound **34** exists as two tautomers. In tautomer **B**, the pyridine ring loses aromaticity and becomes more susceptible to reduction as usual (though conjugated) alkene. Nevertheless, despite our conclusions, the reaction turned out to be chemoselective giving compound **35** as the only product. Our observations are fully supported by other works reporting the same results for various 4-hydroxyquinolines in the presence of different catalytic systems [66, 67]. So far, a reasonable explanation of the experimental results is not available.

The last part of the paper discloses three amusing instances of the hydrogenation where other functionalities were involved.

The first reaction is the hydrogenation of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxylic acid (**37**) (Scheme 14). It was quite curious to obtain different products **38** and **39** while utilizing identical reaction conditions. If compound **38** was much expectable and desirable in the reaction, the isolation of decarboxylated derivative **39** made us feel confused. Even though reductive decarboxylation is a modern technique experiencing intensive investigations [68, 69], its proceeding is unwanted as other synthetic approaches towards compound **38** are complicated

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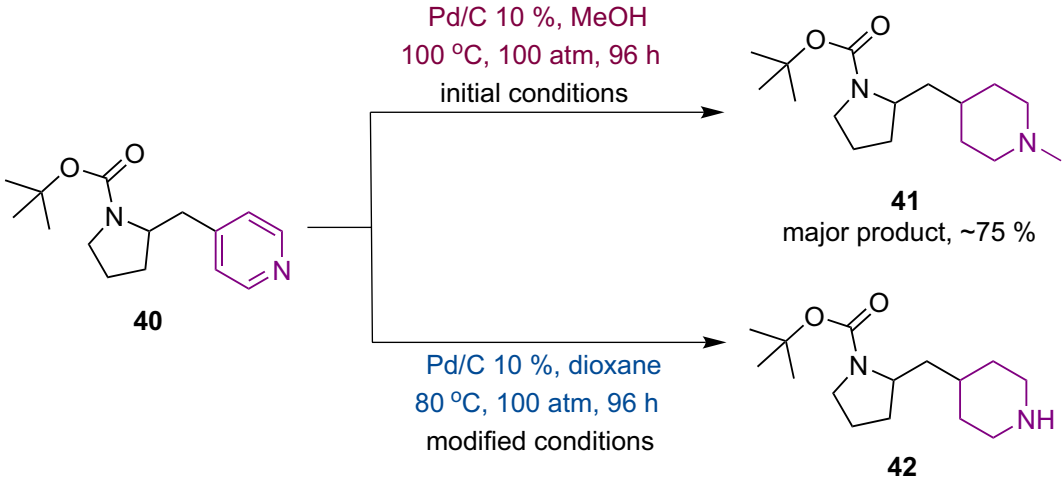
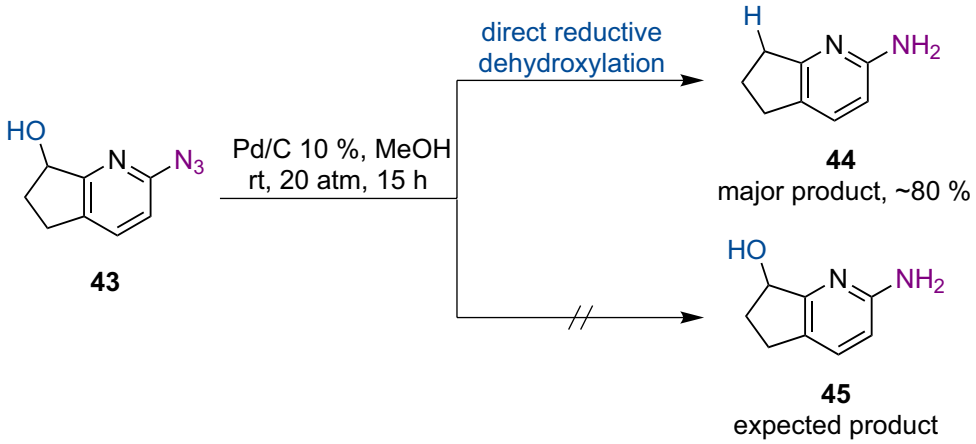


Scheme 15. An unexpected reductive *N*-methylation with methanol



Scheme 16. An unexpected reductive dihydroxylation

and time-consuming [70]. The main question caused by the experiment is "*What is the reason for the decarboxylation and how to ensure that the same Pd-catalyzed reduction conditions give the same result?*". Unfortunately, there is no answer at the moment. We can only assume that the presence of free metal impurities can cause primary decarboxylation of the starting acid **37** followed by reduction.

We observed an undesired *N*-methylation while reducing compound **40** in the methanol solution and producing derivative **41** as a major component in the mixture. The Pd-catalyzed *N*-methylation is already known; it is sometimes used intentionally in order to obtain and simultaneously modify primary or secondary amino groups [71, 72]. To avoid the continuation of this process, we replaced methanol with indifferent 1,4-dioxane, having managed to isolate the target piperidine **42**, which is of interest for medical chemistry and is used in the synthesis of substances having a remarkable activity that inhibits the hepatocyte growth factor receptor, and thus exhibit the antitumor activity, the activity that inhibits angiogenesis, and the activity that inhibits cancer metastasis [73].

The alcohol dehydroxylation is probably one of the fundamental transformations in organic chemistry as it plays a great role in the total synthesis of complex natural products [74]. Recently, several protocols for the reductive dihydroxylation have been published utilizing Ir and Fe catalysts [75, 76]. Palladium is not a common catalyst for the reaction [14]. In this regard, the isolation of dehydroxylated derivative **44** as a main product in the Pd/C catalyzed hydrogenation of azidoalcohol **43** was quite surprising. The formation of such a product shows that the formal debenzylation of **43** is more advantageous than the reduction of the pyridine ring. We are currently working on finding suitable reaction conditions that allow us to purposefully obtain any of the products.

■ Conclusions

Although catalytic hydrogenation reactions are vital transformations for all branches of chemical industry, commercial palladium catalysts are

variable in their fine structure (size of Pd particles, surface morphology, other metals impurities, etc.) and, consequently, in the efficiency, resulting in significant differences in selectivity, reaction times, and yields. In the paper, we have summarized our experience with Pd/C-catalysts from different commercial sources for the hydrogenation reaction and presented cases of unusual reactivity or unexpected outcomes of the reactions encountered in our practice. In general, complications we faced were of three types: (1) irreproducibility of the procedures most likely as the result of a changeable activity of the catalysts; (2) chemoselectivity issues when two or multireducible functional groups were present in the substrate; (3) undesirable Pd-catalyzed defunctionalization reactions. In turn, these complications led to increase in production costs, loss of time and resources. Therefore, because of this variability in the efficiency of Pd catalysts, far more efforts are required to find out the key differences between commercial sources of Pd catalysts, as well as to create protocols clearly defining the catalytic activity of each batch of the catalyst. Moreover, modern chemists need to have clear criteria and regulations of catalysts' quality without wasting precious time and synthetic materials.

■ Experimental part

All starting compounds exposed to hydrogenation were synthesized in Enamine Ltd. and had purity of not less than 95%. Different batches of palladium-containing catalysts used in the experiment were purchased from commercial sources (Daming Ruiheng Chemical Co., Ltd; Hangzhou J & H Chemical Co., Ltd.; Junda Pharm Chem Plant Co., Ltd.; Leap Labchem Co., Ltd; Shanghai Linsai Trade Co., Ltd.; SLN Pharmachem) within a period of 2011–2022. The solvents were distilled prior to the use. If needed, the reactions progress was monitored by ^{1}H NMR spectroscopy. The melting points were measured in open capillary tubes and given uncorrected. ^{1}H NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (500 MHz), or a Varian Unity Plus 400 spectrometer (400 MHz) in a DMSO-d_6, $CDCl_3$ or D_2O solution using tetramethylsilane as an internal standard. Chemical shifts were expressed in δ (ppm) units with the following description: *s* was for a singlet, *d* – a doublet, *t* – a triplet, *q* – a quartet, *p* – a pentet, *m* – a multiplet, *br.* – broadened. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (an atmospheric pressure electrospray ionization (ES-API)) and an Agilent 5890 Series II 5972 GCMS instrument (an electron impact ionization (EI)). Chromatographic experiments revealed the purity of all tested compounds being not less than 95%. The elemental analysis was carried out in the Analytical Chemistry Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine.

Ethyl 5-methyltetrahydrofuran-3-carboxylate (2)

The solution of ethyl 5-methylfuran-3-carboxylate (**1**) (100 g, 0.649 mol) in methanol (800 mL) was charged with 10% palladium on carbon (10 g). The mixture was placed in an autoclave and hydrogenated at 80°C and 100 atm of hydrogen for 336 h. The autoclave was vented, after that the catalyst was filtered off. The solvent was removed under reduced pressure to give the title compound.

A colorless oil. Yield – 95.2 g (92.8%). Anal. Calcd for $C_8H_{14}O_3$, %: C 60.74; H 8.92. Found, %: C 60.54; H 8.98. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.21–1.35 (6H, m, 2×CH_3); 1.77 (1H, dt, J = 12.5, 8.6 Hz, H-4^{fur}); 2.27 (1H, ddd, J = 12.0, 8.7, 5.6 Hz, H-4^{fur}); 3.11 (1H, qd, J = 8.3, 5.7 Hz, H-3^{fur}); 3.86–4.03 (2H, m, H-2^{fur}+H-5^{fur}); 4.09 (1H, dd, J = 8.8, 5.7 Hz, H-2^{fur}); 4.16 (2H, q, J = 7.1 Hz, O$\underline{CH_2}CH_3$). LC-MS (ES-API), *m*/*z*: 159.1 $[M+H]^+$.

4-Amino-3-methoxypyridine 1-oxide (4)

To the solution of 3-methoxy-4-nitropyridine 1-oxide (**3**) (87 g, 0.512 mol) in methanol (1500 mL) 10% strength palladium on carbon (8.7 g) was added. The mixture was hydrogenated in an autoclave at 50°C and 50 atm of hydrogen for 72 h. The catalyst was then filtered off, and the solvent was removed under reduced pressure to give the title compound.

A red solid. Yield – 68.13 g (95.1%). Anal. Calcd for $C_6H_8N_2O_2$, %: C 51.42; H 5.75; N 19.99. Found, %: C 51.20; H 5.81; N 20.13. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.79 (3H, s, OCH_3); 5.83 (2H, s, NH_2); 6.49 (1H, d, J = 6.8 Hz, H-5^{pyr}); 7.56 (1H, dd, J = 6.8, 1.9 Hz, H-6^{pyr}); 7.75 (1H, d, J = 2.0 Hz, H-2^{pyr}). LC-MS (ES-API), *m*/*z*: 141.0 $[M+H]^+$.

3-Methoxypyridin-4-amine (5)

To the solution of 3-methoxy-4-nitropyridine 1-oxide (**3**) (84.8 g, 0.499 mol) in methanol (1500 mL) 20% strength palladium hydroxide on carbon (8.5 g) was added. The mixture was hydrogenated in an autoclave at 50°C and 100 atm of hydrogen for 120 h. After full conversion of the starting compound the autoclave was vented, and the

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catalyst was filtered off. The solvent was then removed under reduced pressure to give the target compound.

A brown powder. Yield – 60.18 g (97.3%). M. p. 88–90°C. Anal. Calcd for $C_6H_8N_2O$, %: C 58.05; H 6.50; N 22.57. Found, %: C 58.23; H 6.36; N 22.72. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.80 (3H, s, OCH_3); 5.64 (2H, s, NH_2); 6.53 (1H, d, J = 5.2 Hz, H-5^{pyr}); 7.73 (1H, d, J = 5.2 Hz, H-6^{pyr}); 7.87 (1H, s, H-2^{pyr}). LC-MS (ES-API), m/z: 125.0 $[M+H]^+$.

1-Oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (7)

1-Oxo-1,2-dihydroisoquinoline-4-carboxylic acid (**6**) (70 g, 0.367 mol) was dissolved in 3500 mL of a water solution of NaOH (14.69 g, 0.367 mol) and 10% strength palladium on carbon (7 g) was then added. The mixture was placed in an autoclave and hydrogenated at 50°C and 50 atm of hydrogen for 168 h. The autoclave was vented, after that the catalyst was filtered off, and the filtrate was acidified with sodium bisulfate. The precipitate formed was filtered off, and the crude product was recrystallized from isopropyl alcohol.

A white solid. Yield – 21.61 g (30.5%). M. p. 218–220°C. Anal. Calcd for $C_{10}H_9NO_3$, %: C 62.82; H 4.75; N 7.33. Found, %: C 62.97; H 4.83; N 7.17. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 3.54–3.68 (2H, m, CH_2); 3.83–3.95 (1H, m, CH); 7.35–7.41 (2H, m, ArH); 7.51 (1H, t, J = 7.7 Hz, ArH); 7.83 (1H, d, J = 7.9 Hz, ArH); 7.94 (1H, d, J = 5.5 Hz, NH); 12.85 (1H, br. s, COOH). LC-MS (ES-API), m/z: 192.1 $[M+H]^+$.

4-(*o*-Tolyl)butanoic acid (9)

4-Oxo-4-(*o*-tolyl)butanoic acid (**8**) (85 g, 0.443 mol) was dissolved in acetic acid (800 mL) followed by adding 10% palladium on carbon (8.5 g), and the mixture was hydrogenated at room temperature and 80 atm of hydrogen for 24 h. After completion of the reaction the solid was filtered off, the solvent was removed under reduced pressure, and the residue was recrystallized from hexane.

A white fluffy solid. Yield – 75.1 g (95.3%). M. p. 55–57°C. Anal. Calcd for $C_{11}H_{14}O_2$, %: C 74.13; H 7.92. Found, %: C 74.01; H 8.05. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.74 (2H, p, J = 7.5 Hz, $CH_2C\underline{H}_2CH_2$); 2.17–2.31 (5H, m, CH_3Ar+CH_2Ar); 2.53–2.60 (2H, m, $C\underline{H}_2COOH$); 7.00–7.16 (4H, m, ArH); COOH proton is in exchange. LC-MS (ES-API), m/z: 177.2 $[M-H]^-$.

3-Aminocyclohexane-1-sulfonic acid (11)

To the solution of 3-aminobenzenesulfonic acid (**10**) (20 g, 0.116 mol) in acetic acid (400 mL) 20% palladium hydroxide on carbon (2.0 g) was added. The mixture was then hydrogenated at 120°C and 120 atm of hydrogen for 48 h. After the reaction was completed, the solid was filtered off, and the solvent was removed under reduced pressure. The residue was treated with methanol to give the title product.

A white powder. Yield – 7.8 g (37.7%). M. p. 232–234°C. Anal. Calcd for $C_6H_{13}NO_3S$, %: C 40.21; H 7.31; N 7.81. Found, %: C 40.39; H 7.16; N 7.72. ^{1}H NMR (400 MHz, D_2O), δ, ppm: 1.23–2.63 (8H, m); 2.80–3.95 (2H, m). LC-MS (ES-API), m/z: 180.2 $[M+H]^+$.

1-(*tert*-Butoxycarbonyl)-3-(hydroxymethyl)azetidine-3-carboxylic acid (13)

3-((Benzyloxy)methyl)-1-(*tert*-butoxycarbonyl)-azetidine-3-carboxylic acid (**12**) (130 g, 0.405 mol) was dissolved in methanol (1500 mL) and 20% palladium hydroxide on carbon (13 g) was added to the solution. The mixture was placed in an autoclave and hydrogenated at 70°C and 100 atm of hydrogen for 15 h. After cooling the autoclave was vented, the catalyst was filtered off, and the solvent was removed under reduced pressure. The residue was treated with isopropyl alcohol to give the title product.

A white solid. Yield – 87.27 g (93%). M. p. 175–177°C. Anal. Calcd for $C_{10}H_{17}NO_5$, %: C 51.94; H 7.41; N 6.06. Found, %: C 52.08; H 7.32; N 6.14. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.35 (9H, s, 3×CH_3); 3.65 (2H, s, CH_2O); 3.73–4.00 (4H, m, 2×CH_2N); COOH and OH protons are in exchange. LC-MS (ES-API), m/z: 230.2 $[M-H]^-$.

(1,4-Oxazepan-7-yl)methanol (15)

The solution of (4-benzyl-1,4-oxazepan-7-yl)-methanol (**14**) (75 g, 0.339 mol) in methanol (1500 mL) containing 20% palladium hydroxide on carbon (7.5 g) was hydrogenated in an autoclave at 50°C and 50 atm of hydrogen for 120 h. After the reaction was completed, the catalyst was filtered off, and the solvent was removed under reduced pressure to give the title compound as an oil.

A pink yellow oil. Yield – 43.43 g (97.7%). Anal. Calcd for $C_6H_{13}NO_2$, %: C 54.94; H 9.99; N 10.68. Found, %: C 55.11; H 10.09; N 10.48. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.49–1.65 (1H, m); 1.73–1.90 (1H, m); 1.95–2.08 (2H, m); 2.75–3.10 (4H, m); 3.32–3.50 (2H, m); 3.51–3.68 (1H, m); 3.69–3.85 (1H, m); 3.88–4.05 (1H, m). LC-MS (ES-API), m/z: 132.2 $[M+H]^+$.

Methyl 3-fluoropyrrolidine-3-carboxylate hydrochloride (17)

To the solution of methyl 1-benzyl-3-fluoropyrrolidine-3-carboxylate hydrochloride (**16**)

(175 g, 0.641 mol) in methanol (1500 mL) 20% palladium on carbon (13 g) was added. The mixture was hydrogenated at 50°C and 100 atm of hydrogen for 12 h. The autoclave was vented, and the catalyst was filtered off. The solvent was removed under reduced pressure to give the title compound.

A yellow powder. Yield – 110.5 g (94.2%). M. p. 153–155°C. Anal. Calcd for $C_6H_{11}ClFNO_2$, %: C 39.25; H 6.04; N 7.63. Found, %: C 39.41; H 6.10; N 7.82. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.28–2.47 (2H, m); 3.24–3.34 (1H, m); 3.42–3.68 (3H, m); 3.77 (3H, s, OCH_3); 10.25 (2H, s, NH_2);. LC-MS (ES-API), m/z: 148.1 $[M-Cl]^+$.

(*S*)-4-(Cyclohexylmethyl)-6-methylmorpholin-3-one (19)

The title compound was prepared according to the procedure given below. Although the structure of the reaction product, as well as its purity, was confirmed while analyzing an aliquot by ^{1}H NMR and LC-MS methods, it was not isolated by the reason of low prospects for further modification.

(*S*)-4-Benzyl-6-methylmorpholin-3-one (**18**) (74 g, 0.361 mol) was dissolved in methanol (800 mL) and 10% palladium on carbon (7.4 g) was then added. The mixture was exposed to hydrogenation at 100°C and 50 atm of hydrogen for 48 h. When the time was over, a 20 mL aliquot of the solution was taken, the solvent was evaporated, and the residue was analyzed by ^{1}H NMR and LC-MS methods.

^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 0.78–0.96 (2H, m, CH^{chex}); 1.06–1.25 (6H, m, CH_3+CH^{chex}); 1.51–1.75 (6H, m, CH^{chex}); 3.00–3.26 (4H, m, 2×CH_2N); 3.85 (1H, dqd, J = 9.1, 6.1, 3.1 Hz, $CH_3C\underline{H}$); 4.02 (2H, s, CH_2O). LC-MS (ES-API), m/z: 212.1 $[M+H]^+$.

Methyl 2-(4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)acetate (22)

To the solution of methyl 2-(4-(benzyloxy)-1*H*-indol-3-yl)acetate (**21**) (5 g, 0.017 mol) in methanol (100 mL) 10% palladium on carbon (0.5 g) was added. The mixture was hydrogenated at 50°C and 100 atm of hydrogen for 48 h. Then the catalyst was filtered off, and the solvent was removed under reduced pressure. The residue was treated with isopropyl alcohol to give the title compound.

A brown powder. Yield – 1.65 g (47%). Anal. Calcd for $C_{11}H_{13}NO_3$, %: C 63.76; H 6.32; N 6.76. Found, %: C 63.54; H 6.43; N 6.87. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.97 (2H, p, J = 6.1 Hz, H-6); 2.21 – 2.30 (2H, m, H-7); 2.71 (2H, t, J = 6.1 Hz, H-5); 3.55 (3H, s, CH_3); 3.62 (2H, s, CH_2CO); 6.58 (1H, d, J = 2.0 Hz, H-2); 11.14 (1H, s, NH). LC-MS (ES-API), m/z: 208.1 $[M+H]^+$.

Methyl 5-methyl-2,3-dihydrobenzofuran-7-carboxylate (25)

Methyl 5-methylbenzofuran-7-carboxylate (**24**) (52 g, 0.274 mol) was dissolved in methanol (1000 mL), and the solution was charged with 10% palladium on charcoal (5.2 g). The mixture was hydrogenated in an autoclave at 50°C and 80 atm of hydrogen for 108 h. The resulting mixture was filtered, and the filtrate was evaporated *in vacuo* to give the target compound.

A white powder. Yield – 49.2 g (93.6%). Anal. Calcd for $C_{11}H_{12}O_3$, %: C 68.74; H 6.29. Found, %: C 68.52; H 6.38. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.23 (3H, s, CH_3Ar); 3.14 (2H, t, J = 8.8 Hz, CH_2Ar); 3.77 (3H, s, OCH_3); 4.57 (2H, t, J = 8.8 Hz, OCH_2); 7.24 (1H, s, ArH); 7.37 (1H, s, ArH). LC-MS (ES-API), m/z: 193.1 $[M+H]^+$.

2-Methyl-5,6,7,8-tetrahydroquinolin-4(1*H*)-one (35)

The solution of 2-methylquinolin-4-ol (**34**) (150 g, 0.943 mol) in methanol (1500 mL) was charged with 10% strength palladium on carbon (15 g). The resulting mixture was hydrogenated at 50°C and 50 atm of hydrogen for 48 h. After the time was over, the solid was filtered off, and the filtrate was evaporated to dryness in a vacuum evaporator to give the title compound.

A beige powder. Yield – 149 g (96.9%). M. p. 239–241°C. Anal. Calcd for $C_{10}H_{13}NO$, %: C 73.59; H 8.03; N 8.58. Found, %: C 73.71; H 7.92; N 8.54. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.53–1.71 (5H, m); 2.11 (3H, s, CH_3); 2.18–2.26 (3H, m); 5.75 (1H, s, H-3); 10.88 (1H, s, NH). LC-MS (ES-API), m/z: 164.2 $[M+H]^+$.

Octahydropyrrolo[1,2-*a*]pyrazine-1-carboxylic acid (38) and octahydropyrrolo[1,2-*a*]pyrazine (39)

The title compounds turned out to be the products of the hydrogenation reaction utilizing the same starting compound and the same conditions (given below), but using different batches of 20% $Pd(OH)_2$/C catalyst. The loadings of the initial pyrrole were 0.5 g to have octahydropyrrolo[1,2-*a*]pyrazine and 3.2 g for octahydropyrrolo[1,2-*a*] pyrazine-1-carboxylic acid. The procedure below is given for an occasion of the decarboxylated derivative; for another product, the quantities are proportional.

The solution of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxylic acid (**37**) (0.5 g, 0.003 mol) in water (10 mL) was loaded with 20% palladium

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hydroxide on carbon (0.05 g), and the mixture was hydrogenated at 100°C and 100 atm of hydrogen for 12 h. After completion of the reaction the catalyst was filtered off, and the solvent was evaporated under reduced pressure providing the title compound.

Octahydropyrrolo[1,2-a]pyrazine-1-carboxylic acid (**38**)

A white powder. Yield – 3.11 g (95%). Anal. Calcd for $C_8H_{14}N_2O_2$, %: C 56.45; H 8.29; N 16.46. Found, %: C 56.28; H 8.41; N 16.68. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.26 (1H, s); 1.53–1.81 (4H, m); 2.06 (2H, q, J = 8.8 Hz); 2.22 (1H, t, J = 12.0 Hz); 2.76 (1H, t, J = 12.2 Hz); 2.90–3.11 (3H, m); 3.21 (1H, d, J = 11.8 Hz); 8.36 (1H, s, NH^+). LC-MS (ES-API), m/z: 171.1 $[M+H]^+$.

Octahydropyrrolo[1,2-a]pyrazine (**39**)

A colorless oil. Yield – 0.35 g (92%). B. p. 85–88°C (0.03 atm). Anal. Calcd for $C_7H_{14}N_2$, %: C 66.62; H 11.18; N 22.20. Found, %: C 66.73; H 11.05; N 22.38. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.07–1.28 (1H, m); 1.45–1.77 (4H, m); 1.80–2.11 (3H, m); 2.17–2.27 (1H, m); 2.53–2.61 (1H, m); 2.70–2.77 (1H, m); 2.78–2.97 (3H, m). GC-MS (EI), m/z: 126.0 $[M]^+$.

***tert*-Butyl 2-(piperidin-4-ylmethyl)pyrrolidine-1-carboxylate (42)**

tert-Butyl 2-(pyridin-4-ylmethyl)pyrrolidine-1-carboxylate (**40**) (15.15 g, 0.058 mol) was dissolved in 1,4-dioxane (300 mL) followed by adding 10% palladium on carbon (1.5 g) and the mixture was hydrogenated at 80°C and 100 atm of hydrogen for 96 h. After completion of the reaction the solid was filtered off, and the solvent was removed under reduced pressure to give the title compound.

A white powder. Yield – 13.4 g (86.5%). M. p. 73–75°C. Anal. Calcd for $C_{15}H_{28}N_2O_2$, %: C 67.13; H 10.52; N 10.44. Found, %: C 67.32; H 10.44; N 10.58. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 0.95–1.40 (4H, m); 1.46 (9H, s, 3×CH_3); 1.56–2.11 (8H, m); 2.52–2.67 (2H, m); 2.95–3.11 (2H, m); 3.25–3.43 (2H, m); 3.78–3.98 (1H, m). LC-MS (ES-API), m/z: 269.2 $[M+H]^+$.

References

1. Petrov, L. Problems and Challenges About Accelerated Testing of the Catalytic Activity of Catalysts. In *Principles and Methods for Accelerated Catalyst Design and Testing*; Derouane, E. G., Parmon, V., Lemos, F., Ribeiro, F. R., Eds. Springer Netherlands: Dordrecht, 2002; pp 13–69. https://doi.org/10.1007/978-94-010-0554-8_2.
2. Röper, M. Homogene Katalyse in der Chemischen Industrie. Selektivität, Aktivität und Standzeit. *Chem. unserer Zeit* **2006,** *40* (2), 126–135. https://doi.org/10.1002/ciuz.200600373.
3. Zhang, L.; Zhou, M.; Wang, A.; Zhang, T. Selective Hydrogenation over Supported Metal Catalysts: From Nanoparticles to Single Atoms. *Chem. Rev.* **2020,** *120* (2), 683–733. https://doi.org/10.1021/acs.chemrev.9b00230.
4. Meemken, F.; Baiker, A. Recent Progress in Heterogeneous Asymmetric Hydrogenation of C=O and C=C Bonds on Supported Noble Metal Catalysts. *Chem. Rev.* **2017,** *117* (17), 11522–11569. https://doi.org/10.1021/acs.chemrev.7b00272.
5. Wang, D.; Astruc, D. The Golden Age of Transfer Hydrogenation. *Chem. Rev.* **2015,** *115* (13), 6621–6686. https://doi.org/10.1021/acs.chemrev.5b00203.
6. Cai, R.; Ellis, P. R.; Yin, J.; Liu, J.; Brown, C. M.; Griffin, R.; Chang, G.; Yang, D.; Ren, J.; Cooke, K.; Bishop, P. T.; Theis, W.; Palmer, R. E. Performance of Preformed Au/Cu Nanoclusters Deposited on MgO Powders in the Catalytic Reduction of 4-Nitrophenol in Solution. *Small* **2018,** *14* (13), 1703734. https://doi.org/10.1002/smll.201703734.
7. Zhang, S.; Xia, Z.; Ni, T.; Zhang, Z.; Ma, Y.; Qu, Y. Strong electronic metal-support interaction of Pt/CeO2 enables efficient and selective hydrogenation of quinolines at room temperature. *J. Catal.* **2018,** *359*, 101–111. https://doi.org/10.1016/j.jcat.2018.01.004.
8. Deraedt, C.; Ye, R.; Ralston, W. T.; Toste, F. D.; Somorjai, G. A. Dendrimer-Stabilized Metal Nanoparticles as Efficient Catalysts for Reversible Dehydrogenation/Hydrogenation of N-Heterocycles. *J. Am. Chem. Soc.* **2017,** *139* (49), 18084–18092. https://doi.org/10.1021/jacs.7b10768.
9. Prechtl, M. H. G.; Scariot, M.; Scholten, J. D.; Machado, G.; Teixeira, S. R.; Dupont, J. Nanoscale Ru(0) Particles: Arene Hydrogenation Catalysts in Imidazolium Ionic Liquids. *Inorg. Chem.* **2008,** *47* (19), 8995–9001. https://doi.org/10.1021/ic801014f.
10. Tamura, M.; Yonezawa, D.; Oshino, T.; Nakagawa, Y.; Tomishige, K. In Situ Formed Fe Cation Modified Ir/MgO Catalyst for Selective Hydrogenation of Unsaturated Carbonyl Compounds. *ACS Catalysis* **2017,** *7* (8), 5103–5111. https://doi.org/10.1021/acscatal.7b01055.
11. Ayass, W. W.; Miñambres, J. F.; Yang, P.; Ma, T.; Lin, Z.; Meyer, R.; Jaensch, H.; Bons, A.-J.; Kortz, U. Discrete Polyoxopalladates as Molecular Precursors for Supported Palladium Metal Nanoparticles as Hydrogenation Catalysts. *Inorg. Chem.* **2019,** *58* (9), 5576–5582. https://doi.org/10.1021/acs.inorgchem.8b03513.
12. Stoffels, M. A.; Klauck, F. J. R.; Hamadi, T.; Glorius, F.; Leker, J. Technology Trends of Catalysts in Hydrogenation Reactions: A Patent Landscape Analysis. *Adv. Synth. Catal.* **2020,** *362* (6), 1258–1274. https://doi.org/10.1002/adsc.201901292.
13. Nerozzi, F. Heterogeneous Catalytic Hydrogenation. *Platinum Met. Rev.* **2012,** *56* (4), 236–241. https://doi.org/10.1595/147106712X654187.
14. King, A. O.; Larsen, R. D.; Negishi, E.-I. Palladium-Catalyzed Heterogeneous Hydrogenation. In *Handbook of Organopalladium Chemistry for Organic Synthesis*, 2002; pp 2719–2752. https://doi.org/10.1002/0471212466.ch124.
15. Baimuratova, R. K.; Andreeva, A. V.; Uflyand, I. E.; Shilov, G. V.; Bukharbayeva, F. U.; Zharmagambetova, A. K.; Dzhardimalieva, G. I. Synthesis and Catalytic Activity in the Hydrogenation Reaction of Palladium-Doped Metal-Organic Frameworks Based on Oxo-Centered Zirconium Complexes. *Journal of Composites Science* **2022,** *6* (10), 299. https://doi.org/10.3390/jcs6100299.
16. Rao, R. G.; Blume, R.; Hansen, T. W.; Fuentes, E.; Dreyer, K.; Moldovan, S.; Ersen, O.; Hibbitts, D. D.; Chabal, Y. J.; Schlögl, R.; Tessonnier, J.-P. Interfacial charge distributions in carbon-supported palladium catalysts. *Nature Communications* **2017,** *8* (1), 340. https://doi.org/10.1038/s41467-017-00421-x.

17. Iost, K. N.; Borisov, V. A.; Temerev, V. L.; Surovikin, Y. V.; Pavluchenko, P. E.; Trenikhin, M. V.; Arbuzov, A. B.; Shlyapin, D. A.; Tsyrulnikov, P. G.; Vedyagin, A. A. Carbon support hydrogenation in Pd/C catalysts during reductive thermal treatment. *Int. J. Hydrogen Energy* **2018,** *43* (37), 17656–17663. https://doi.org/10.1016/j.ijhydene.2018.07.182.
18. Campanati, M.; Fornasari, G.; Vaccari, A. Fundamentals in the preparation of heterogeneous catalysts. *Catal. Today* **2003,** *77* (4), 299–314. https://doi.org/10.1016/S0920-5861(02)00375-9.
19. Albers, P. W.; Möbus, K.; Wieland, S. D.; Parker, S. F. The fine structure of Pearlman's catalyst. *Phys. Chem. Chem. Phys.* **2015,** *17* (7), 5274–5278. https://doi.org/10.1039/C4CP05681G.
20. Crawford, C. J.; Qiao, Y.; Liu, Y.; Huang, D.; Yan, W.; Seeberger, P. H.; Oscarson, S.; Chen, S. Defining the Qualities of High-Quality Palladium on Carbon Catalysts for Hydrogenolysis. *Org. Process Res. Dev.* **2021,** *25* (7), 1573–1578. https://doi.org/10.1021/acs.oprd.0c00536.
21. Ivanytsia, M. O.; Lytvynenko, A. S.; Tverdyi, D. O.; Burianov, V. V.; Sotnik, S. O.; Kolotilov, S. V.; Riabukhin, S. V.; Volochniuk, D. M. Sposib otsinky aktyvnosti katalizatoriv reaktsii hidruvannia orhanichnykh spoluk [A method of evaluating the activity of catalysts for reactions of hydrogenation of organic compounds, *in Ukrainian*]. UA Patent 124641, Oct 20, 2021.
22. Mousavi, S.; Nazari, B.; Keshavarz, M. H.; Bordbar, A.-K. A Simple Method for Safe Determination of the Activity of Palladium on Activated Carbon Catalysts in the Hydrogenation of Cinnamic Acid to Hydrocinnamic Acid. *Ind. Eng. Chem. Res.* **2020,** *59* (5), 1862–1874. https://doi.org/10.1021/acs.iecr.9b06087.
23. Stamm, S.; Linden, A.; Heimgartner, H. Chiral Heterospirocyclic 2*H*-Azirin-3-amines as Synthons for 3-Amino-2,3,4,5-tetrahydrofuran-3-carboxylic Acid and Their Use in Peptide Synthesis. *Helv. Chim. Acta* **2003,** *86* (5), 1371–1396. https://doi.org/10.1002/hlca.200390124.
24. Soldermann, C. P.; Quancard, J.; Schlapbach, A.; Simic, O.; Tintelnot-Blomley, M.; Zoller, Th. Novel pyrazolo pyrimidine derivatives and their use as malt1 inhibitors. WO2015181747A1, Dec 3, 2015.
25. Peters, O.; Haaf, K. B.; Lindell, S. D.; Bojack, G.; Law, K. R.; Machettira, A. B.; Dietrich, H.; Gatzweiler, E.; Rosinger, Ch. H. Herbicidally active 3-phenylisoxazoline-5-carboxamides of tetrahydro and dihydrofuran carboxylic acids and esters. US2021292312A1, Sep 23, 2021.
26. Zhou, W.; Peng, Y.; Li, S.-S. Semi-synthesis and anti-tumor activity of 5,8-O-dimethyl acylshikonin derivatives. *Eur. J. Med. Chem.* **2010,** *45* (12), 6005–6011. https://doi.org/10.1016/j.ejmech.2010.09.068.
27. Mao, Z.; Gu, H.; Lin, X. Recent Advances of Pd/C-Catalyzed Reactions. *Catalysts* **2021**, *11*, 1078. https://doi.org/10.3390/catal11091078.
28. Wu, Z.-Q.; Jiang, X.-K.; Li, Z.-T. Hydrogen bonding-mediated self-assembly of square and triangular metallocyclophanes. *Tetrahedron Lett.* **2005,** *46* (46), 8067–8070. https://doi.org/10.1016/j.tetlet.2005.06.173.
29. Barraclough, P.; Black, J. W.; Cambridge, D.; Collard, D.; Firmin, D.; Gerskowitch, V. P.; Glen, R. C.; Giles, H.; Hill, A. P. Inotropic 'A' ring substituted sulmazole and isomazole analogs. *J. Med. Chem.* **1990,** *33* (8), 2231–2239. 10.1021/jm00170a030.
30. Plaquevent, J.-C.; Chichaoui, I. Réduction régiospécifique des bipyridines. *Tetrahedron Lett.* **1993,** *34* (33), 5287–5288. https://doi.org/10.1016/S0040-4039(00)73975-X.
31. Mondal, J.; Trinh, Q. T.; Jana, A.; Ng, W. K. H.; Borah, P.; Hirao, H.; Zhao, Y. Size-Dependent Catalytic Activity of Palladium Nanoparticles Fabricated in Porous Organic Polymers for Alkene Hydrogenation at Room Temperature. *ACS Applied Materials & Interfaces* **2016,** *8* (24), 15307–15319. https://doi.org/10.1021/acsami.6b03127.
32. Frackenpohl, J.; Zeiss, H.-J.; Heinemann, I.; Willms, L.; Müller, Th.; Busch, M.; Von Koskull-Döering, P.; Rosinger, Ch. H.; Dittgen, J.; Hills, M. J. Use of substituted isoquinolinones, isoquinolindiones, isoquinolintriones and dihydroisoquinolinones or in each case salts thereof as active agents against abiotic stress in plants. US2014302987A1, Oct 9, 2014.
33. Yu, Y.; Guo, J.; Cai, Z.; Ju, Y.; Xu, J.; Gu, Q.; Zhou, H. Identification of new building blocks by fragment screening for discovering GyrB inhibitors. *Bioorg. Chem.* **2021,** *114*, 105040. https://doi.org/10.1016/j.bioorg.2021.105040.
34. Baumann, K.; Knapp, H.; Strnadt, G.; Schulz, G.; Grassberger, M. A. Carbonyl to methylene conversions at the tricarbonyl-portion of ascomycin derivatives. *Tetrahedron Lett.* **1999,** *40* (44), 7761–7764. https://doi.org/10.1016/S0040-4039(99)01622-6.
35. Clive, D. L. J.; Wang, J. A Tin Hydride Designed To Facilitate Removal of Tin Species from Products of Stannane-Mediated Radical Reactions. *J. Org. Chem.* **2002,** *67* (4), 1192–1198. https://doi.org/10.1021/jo010885c.
36. Vannice, M. A.; Poondi, D. The Effect of Metal-Support Interactions on the Hydrogenation of Benzaldehyde and Benzyl Alcohol. *J. Catal.* **1997,** *169* (1), 166–175. https://doi.org/10.1006/jcat.1997.1696.
37. Wang, W.; Yang, Y.; Luo, H.; Hu, T.; Liu, W. Amorphous Co–Mo–B catalyst with high activity for the hydrodeoxygenation of bio-oil. *Catal. Commun.* **2011,** *12* (6), 436–440. https://doi.org/10.1016/j.catcom.2010.11.001.
38. Zaccheria, F.; Ravasio, N.; Ercoli, M.; Allegrini, P. Heterogeneous Cu-catalysts for the reductive deoxygenation of aromatic ketones without additives. *Tetrahedron Lett.* **2005,** *46* (45), 7743–7745. https://doi.org/10.1016/j.tetlet.2005.09.041.
39. Argouarch, G. Mild and efficient rhodium-catalyzed deoxygenation of ketones to alkanes. *New J. Chem.* **2019,** *43* (28), 11041–11044. https://doi.org/10.1039/C9NJ02954K.
40. Volkov, A.; Gustafson, K. P. J.; Tai, C.-W.; Verho, O.; Bäckvall, J.-E.; Adolfsson, H. Mild Deoxygenation of Aromatic Ketones and Aldehydes over Pd/C Using Polymethylhydrosiloxane as the Reducing Agent. *Angew. Chem. Int. Ed.* **2015,** *54* (17), 5122–5126. https://doi.org/10.1002/anie.201411059.
41. Bejblová, M.; Zámostný, P.; Červený, L.; Čejka, J. Hydrodeoxygenation of benzophenone on Pd catalysts. *Applied Catalysis A: General* **2005,** *296* (2), 169–175. https://doi.org/10.1016/j.apcata.2005.07.061.
42. Gong, S. W.; He, H. F.; Zhao, C. Q.; Liu, L. J.; Cui, Q. X. Convenient Deoxygenation of Aromatic Ketones by Silica-Supported Chitosan Schiff Base Palladium Catalyst. *Synth. Commun.* **2012,** *42* (4), 574–581. https://doi.org/10.1080/00397911.2010.527423.
43. Newman, M. S.; Cline, W. K. A new synthesis of 2,9-dimethylpicene. *J. Org. Chem.* **1951,** *16* (6), 934–940. https://doi.org/10.1021/jo01146a017.
44. Uysal, T.; Cosford, N. D. P. Compounds and methods for treatment of disorders associated with er stress. WO2007111994A2, Oct 4, 2007.
45. Egli, R.; Eugster, C. H. Über die selektive katalytische Reduktion von substituierten Anilinen zu substituierten Cyclohexylaminen und von Benzol- bzw. Phenyl-alkan-sulfonsäuren zu Cyclohexan- bzw. Cyclohexylalkan-sulfonsäuren. *Helv. Chim. Acta* **1975,** *58* (8), 2321–2346. https://doi.org/10.1002/hlca.19750580814.
46. Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons, 2006. https://doi.org/10.1002/0470053488.
47. Guazzelli, L.; Crawford, C. J.; Ulc, R.; Bowen, A.; McCabe, O.; Jedlicka, A. J.; Wear, M. P.; Casadevall, A.; Oscarson, S. A synthetic glycan array containing Cryptococcus neoformans glucuronoxylomannan capsular polysaccharide fragments allows the mapping of protective epitopes. *Chemical Science* **2020,** *11* (34), 9209–9217. https://doi.org/10.1039/D0SC01249A.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

48. Boutet, J.; Blasco, P.; Guerreiro, C.; Thouron, F.; Dartevelle , S.; Nato , F.; Cañada, F. J.; Ardá, A.; Phalipon, A.; Jiménez-Barbero, J.; Mulard, L. A. Detailed Investigation of the Immunodominant Role of O-Antigen Stoichiometric O-Acetylation as Revealed by Chemical Synthesis, Immunochemistry, Solution Conformation and STD-NMR Spectroscopy for *Shigella flexneri* 3a. *Chem. Eur. J.* **2016,** *22* (31), 10892–10911. https://doi.org/10.1002/chem.201600567.
49. Zhou, H.; Liao, X.; Cook, J. M. Regiospecific, Enantiospecific Total Synthesis of the 12-Alkoxy-Substituted Indole Alkaloids, (+)-12-Methoxy-Na-methylvellosimine, (+)-12-Methoxyaffinisine, and (−)-Fuchsiaefoline. *Org. Lett.* **2004,** *6* (2), 249–252. https://doi.org/10.1021/ol0362212.
50. Nicolaou, K. C.; Claiborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorensen, E. J. Synthesis of Novel Taxoids. *J. Am. Chem. Soc.* **1994,** *116* (4), 1591–1592. https://doi.org/10.1021/ja00083a063.
51. Kozioł, A.; Lendzion-Paluch, A.; Manikowski, A. A Fast and Effective Hydrogenation Process of Protected Pentasaccharide: A Key Step in the Synthesis of Fondaparinux Sodium. *Org. Process Res. Dev.* **2013,** *17* (5), 869–875. https://doi.org/10.1021/op300367c.
52. NG, P. Y.; Jewett, I.; Lucas, M. C.; Padilla, F.; Enyedy, I. J. 6-substituted-9*H*-purine derivatives and related uses. WO2022178256A1, Aug 25, 2022.
53. Tang, L.; Wu, W.; Zhang, C.; Shi, Z.; Chen, D.; Zhai, X.; Jiang, Y. Discovery of the PARP (poly ADP-ribose polymerase) inhibitor 2-(1-(4,4-difluorocyclohexyl)piperidin-4-yl)-1H-benzo[d]imidazole-4-carboxamide for the treatment of cancer. *Bioorg. Chem.* **2021,** *114*, 105026. https://doi.org/10.1016/j.bioorg.2021.105026.
54. Li, Y.; Manickam, G.; Ghoshal, A.; Subramaniam, P. More Efficient Palladium Catalyst for Hydrogenolysis of Benzyl Groups. *Synth. Commun.* **2006,** *36* (7), 925–928. https://doi.org/10.1080/00397910500466199.
55. Faust, M. R.; Höfner, G.; Pabel, J.; Wanner, K. T. Azetidine derivatives as novel γ-aminobutyric acid uptake inhibitors: Synthesis, biological evaluation, and structure–activity relationship. *Eur. J. Med. Chem.* **2010,** *45* (6), 2453–2466. https://doi.org/10.1016/j.ejmech.2010.02.029.
56. Védrine, J. C. Metal Oxides in Heterogeneous Oxidation Catalysis: State of the Art and Challenges for a More Sustainable World. *ChemSusChem* **2019,** *12* (3), 577–588. https://doi.org/10.1002/cssc.201802248.
57. Grice, P.; Ley, S. V.; Pietruszka, J.; Osborn, H. M. I.; Priepke, H. W. M.; Warriner, S. L. A New Strategy for Oligosaccharide Assembly Exploiting Cyclohexane-1,2-diacetal Methodology: An Efficient Synthesis of a High Mannose Type Nonasaccharide. *Chem. Eur. J.* **1997,** *3* (3), 431–440. https://doi.org/10.1002/chem.19970030315.
58. Crawford, C.; Oscarson, S. Optimized Conditions for the Palladium-Catalyzed Hydrogenolysis of Benzyl and Naphthylmethyl Ethers: Preventing Saturation of Aromatic Protecting Groups. *Eur. J. Org. Chem.* **2020,** *2020* (22), 3332–3337. https://doi.org/10.1002/ejoc.202000401.
59. Shao, J.; Zhu, K.; Du, D.; Zhang, Y.; Tao, H.; Chen, Z.; Jiang, H.; Chen, K.; Luo, C.; Duan, W. Discovery of 2-substituted-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide as potent and selective protein arginine methyltransferases 5 inhibitors: Design, synthesis and biological evaluation. *Eur. J. Med. Chem.* **2019,** *164*, 317–333. https://doi.org/10.1016/j.ejmech.2018.12.065.
60. Schudok, M.; Matter, H.; Hofmeister, A. Tetrahydrofurane derivatives for use as inhibitors of matrix metalloproteinases. WO2006077013A1, Jul 27, 2006.
61. Armour, D. R.; Chung, K. M. L.; Congreve, M.; Evans, B.; Guntrip, S.; Hubbard, T.; Kay, C.; Middlemiss, D.; Mordaunt, J. E.; Pegg, N. A.; Vinader, M. V.; Ward, P.; Watson, S. P. Tetrazole NK1 receptor antagonists: The identification of an exceptionally potent orally active antiemetic compound. *Bioorg. Med. Chem. Lett.* **1996,** *6* (9), 1015–1020. https://doi.org/10.1016/0960-894X(96)00163-1.
62. Wagener, T.; Heusler, A.; Nairoukh, Z.; Bergander, K.; Daniliuc, C. G.; Glorius, F. Accessing (Multi)Fluorinated Piperidines Using Heterogeneous Hydrogenation. *ACS Catalysis* **2020,** *10* (20), 12052–12057. https://doi.org/10.1021/acscatal.0c03278.
63. Zhu, J.; Chen, P.-H.; Lu, G.; Liu, P.; Dong, G. Ruthenium-Catalyzed Reductive Cleavage of Unstrained Aryl–Aryl Bonds: Reaction Development and Mechanistic Study. *J. Am. Chem. Soc.* **2019,** *141* (46), 18630–18640. https://doi.org/10.1021/jacs.9b11605.
64. Kim, S.; Loose, F.; Bezdek, M. J.; Wang, X.; Chirik, P. J. Hydrogenation of N-Heteroarenes Using Rhodium Precatalysts: Reductive Elimination Leads to Formation of Multimetallic Clusters. *J. Am. Chem. Soc.* **2019,** *141* (44), 17900–17908. https://doi.org/10.1021/jacs.9b09540.
65. Yu, T.; Wang, J.; Li, X.; Cao, X.; Gu, H. An Improved Method for the Complete Hydrogenation of Aromatic Compounds under 1 Bar H2 with Platinum Nanowires. *ChemCatChem* **2013,** *5* (10), 2852–2855. https://doi.org/10.1002/cctc.201300394.
66. McPhillie, M. J.; Zhou, Y.; Hickman, M. R.; Gordon, J. A.; Weber, C. R.; Li, Q.; Lee, P. J.; Amporndanai, K.; Johnson, R. M.; Darby, H.; Woods, S.; Li, Z.-H.; Priestley, R. S.; Ristroph, K. D.; Biering, S. B.; El Bissati, K.; Hwang, S.; Hakim, F. E.; Dovgin, S. M.; Lykins, J. D.; Roberts, L.; Hargrave, K.; Cong, H.; Sinai, A. P.; Muench, S. P.; Dubey, J. P.; Prud'homme, R. K.; Lorenzi, H. A.; Biagini, G. A.; Moreno, S. N.; Roberts, C. W.; Antonyuk, S. V.; Fishwick, C. W. G.; McLeod, R. Potent Tetrahydroquinolone Eliminates Apicomplexan Parasites. *Frontiers in Cellular and Infection Microbiology* **2020,** *10*. https://doi.org/10.3389/fcimb.2020.00203.
67. Höglund, I. P. J.; Silver, S.; Engström, M. T.; Salo, H.; Tauber, A.; Kyyrönen, H.-K.; Saarenketo, P.; Hoffrén, A.-M.; Kokko, K.; Pohjanoksa, K.; Sallinen, J.; Savola, J.-M.; Wurster, S.; Kallatsa, O. A. Structure−Activity Relationship of Quinoline Derivatives as Potent and Selective α2C-Adrenoceptor Antagonists. *J. Med. Chem.* **2006,** *49* (21), 6351–6363. https://doi.org/10.1021/jm060262x.
68. Matsubara, S.; Yokota, Y.; Oshima, K. Palladium-Catalyzed Decarboxylation and Decarbonylation under Hydrothermal Conditions: Decarboxylative Deuteration. *Org. Lett.* **2004,** *6* (12), 2071–2073. https://doi.org/10.1021/ol0492602.
69. Modak, A.; Maiti, D. Metal catalyzed defunctionalization reactions. *Org. Biomol. Chem.* **2016,** *14* (1), 21–35. https://doi.org/10.1039/C5OB01949D.
70. Hanessian, S.; Sharma, R. The Synthesis of Bicyclic Piperazine-2-carboxylic Acids from L-Proline. *Heterocycles* **2000**, *52* (3), 1231–1239. https://doi.org/10.3987/COM-99-S136.
71. Uozumi, Y.; Shen, G. Pd/C-Catalyzed Reductive N-Methylation of Quinolines. *Synfacts* **2019,** *15* (07), 0790. https://doi.org/10.1055/s-0039-1689752.
72. Goyal, V.; Gahtori, J.; Narani, A.; Gupta, P.; Bordoloi, A.; Natte, K. Commercial Pd/C-Catalyzed N-Methylation of Nitroarenes and Amines Using Methanol as Both C1 and H2 Source. *J. Org. Chem.* **2019,** *84* (23), 15389–15398. https://doi.org/10.1021/acs.joc.9b02141.
73. Matsushima, T.; Takahashi, K.; Funasaka, S.; Obaishi, H.; Shirotori, S. Pyridine derivatives and pyrimidine derivatives. US8288538B2, Oct 16, 2012.
74. Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. Synthesis of Azadirachtin: A Long but Successful Journey. *Angew. Chem. Int. Ed.* **2007,** *46* (40), 7629–7632. https://doi.org/10.1002/anie.200703027.

75. Huang, J.-L.; Dai, X.-J.; Li, C.-J. Iridium-Catalyzed Direct Dehydroxylation of Alcohols. *Eur. J. Org. Chem.* **2013,** *2013* (29), 6496–6500. https://doi.org/10.1002/ejoc.201301293.
76. Chan, L. Y.; Lim, J. S. K.; Kim, S. Iron-Catalyzed Reductive Dehydroxylation of Benzylic Alcohols Using Polymethylhydrosiloxane (PMHS). *Synlett* **2011,** *2011* (19), 2862–2866. https://doi.org/10.1055/s-0031-1289857.

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