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# Rhodium(CAAC)-Catalyzed Arene Hydrogenation of Benzo-Fused *N*-Heterocycles to Saturated Building Blocks with an all-*cis* Configuration

Christian H. Schiwek,[+a] Simone Stegbauer,[+a] Thomas Pickl,[a] and Thorsten Bach[a,*]

[a] Technical University Munich, School of Natural Sciences, Department of Chemistry and Catalysis Research Center, Lichtenbergstrasse 4, 85747 Garching, Germany
E-mail: thorsten.bach@ch.tum.de

[+] These authors contributed equally to this work.

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*Dedicated to Professor Andreas Pfaltz*

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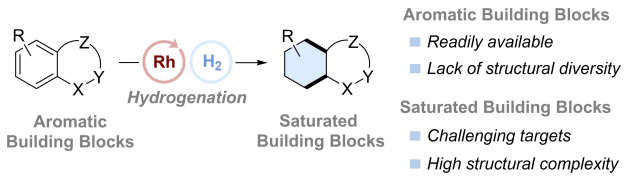
**Abstract:** Saturated carbo- and heterocyclic building blocks can be readily obtained by the hydrogenation of aromatic carbo- and heterocycles. Although a variety of methods have been established to accomplish this transformation for simple arenes, the hydrogenation of aromatic *N*-heterocycles is less explored. We herein report a diastereoselective arene hydrogenation which was applied to an array of benzo-fused *N*-heterocycles. A total of 48 saturated heterocycles was obtained by hydrogenation in the presence of the rhodium complex $^{Cy}$(CAAC)Rh(cod)Cl in yields of 72–98% with moderate to high diastereoselectivities exhibiting the hydrogen atoms in an all-*cis* arrangement. The high tolerance towards functional groups enables the formation of valuable saturated products, which offer a starting point for further derivatization.

**Keywords:** Hydrogenation; Heterocycles; Hydrocarbons; Heterogeneous catalysis; High-pressure chemistry

Heterocycles are among the most important and common substructures within an array of biologically relevant secondary metabolites.[1] The desire to accomplish the structural diversity found in nature is a main driving force in medicinal chemistry research. Against this background, it is not surprising that approximately half of all small-molecule pharmaceuticals or agrochemicals contain an *N*-heterocyclic ring.[2] The transition from aromatic structures to three-dimensional saturated counterparts is extremely valuable for this purpose.[3] Thus, the step-economical access to functionalized saturated *N*-heterocycles along with related structure elements is highly attractive. However, routes to fully saturated *N*-heterocyclic structures are less developed, particularly when starting from simple heteroaromatics.[4] Advances to conquer the three dimensional chemical structure space have been made by several research groups,[5–7] including ourselves.[8] Nevertheless, new methods are being continuously developed, emphasizing the importance of this transformation.[9] In this context, rhodium particles and complexes have established themselves as widely employed catalysts for hydrogenation reactions.[5–8] Still, the arene hydrogenation of *N*-heterocycles remains a challenge in contemporary catalysis due to poisoning by strongly coordinating nitrogen atoms.[10] Furthermore, the presence of weak bonds adjacent to nitrogen atoms or attached to the reactive arene can promote deleterious side reactions. The desire to

escape from chemical flatland inspired us to investigate the arene hydrogenation of several nitrogen containing heterocycles addressing several selectivity issues (chemoselectivity, simple and facial diastereoselectivity) and further exploring the limits of rhodium catalyzed hydrogenation reactions (Scheme 1).

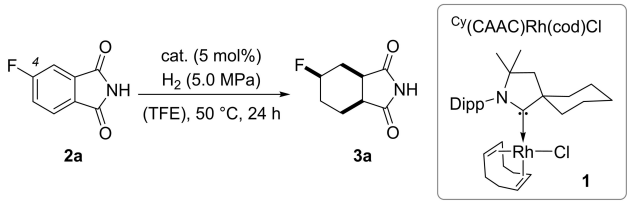
In previous work, we have shown that the known rhodium(I) (pre)catalyst **1**[6,7] with a cyclic (alkyl)(amino)carbene (CAAC) ligand[11] is superior for the selective hydrogenation of 2-oxindoles, 3,4-dihydroquinolones and aromatic 2,5-diketopiperazines.[8] It was revealed by mechanistic studies, that the catalytically active rhodium species is not homogeneous but heterogeneous.[8b,9g,12] In order to demonstrate the potential of catalyst **1** for a broadly applicable arene hydrogenation, our present study




**Scheme 1.** Transition from Planar to Structural Complex Building Blocks by Hydrogenation of *N*-Heteroarenes.

commenced with optimization experiments [gas–liquid chromatography (GLC) analysis] and an evaluation of common commercially available heterogeneous hydrogenation catalysts. These experiments were carried out with phthalimide **2a** as initial substrate. Pd/C, Ru/C, $Ru/Al_2O_3$ and $Rh/Al_2O_3$ showed no reactivity after 24 h using 2,2,2-trifluoroethanol (TFE) as the solvent of choice, 5.0 MPa hydrogen pressure and a reaction temperature of 50 °C (Table 1, entries 1–4). In contrast to the previous catalysts, $PtO_2$ showed full conversion of the starting material **2a** but an undesired hydrodefluorination was the main reaction pathway (Table 1, entry 5). In a similar fashion, Rh/C led also mainly to hydrodefluorination (Table 1, entry 6). Recognizably, Rh/C showed a slightly higher yield and selectivity towards the desired all-*cis* product **3a**, which prompted further investigations. Conspicuously, the homogeneous rhodium complex **1** showed no reactivity in the desired transformation (Table 1, entry 7). Finally, the addition of inorganic 4 Å molecular sieves (MS) to the homogeneous complex **1** drastically increased the yield as well as the selectivity of this transformation and the saturated product **3a** was furnished as single isomer (Table 1, entry 8). Clearly, the rhodium (pre)catalyst **1** showed the highest selectivity, given that a rather labile substituent was retained at the arene core. The molecular sieves are likely required as support for the rhodium particles (*vide infra*).[8b]

**Table 1.** Optimization of the Arene Hydrogenation of 4-Fluorophthalimide (**2a**) by Variation of the Heterogeneous Catalyst.




| #[a] | catalyst | conv.[b] **2a** [%] | yield[b] **3a** [%] | *dr*[b] **3a** |
|---|---|---|---|---|
| 1 | Pd/C | < 5 | – | – |
| 2 | Ru/C | < 5 | – | – |
| 3 | $Ru/Al_2O_3$ | < 5 | – | – |
| 4 | $Rh/Al_2O_3$ | < 5 | – | – |
| 5 | $PtO_2$ | > 99 | 15 | 90:10 |
| 6 | Rh/C | > 99 | 36 | 95:5 |
| 7 | Rh(CAAC) **1** | – | – | – |
| 8[c] | Rh(CAAC) **1** | > 99 | 75 | 99:1 |

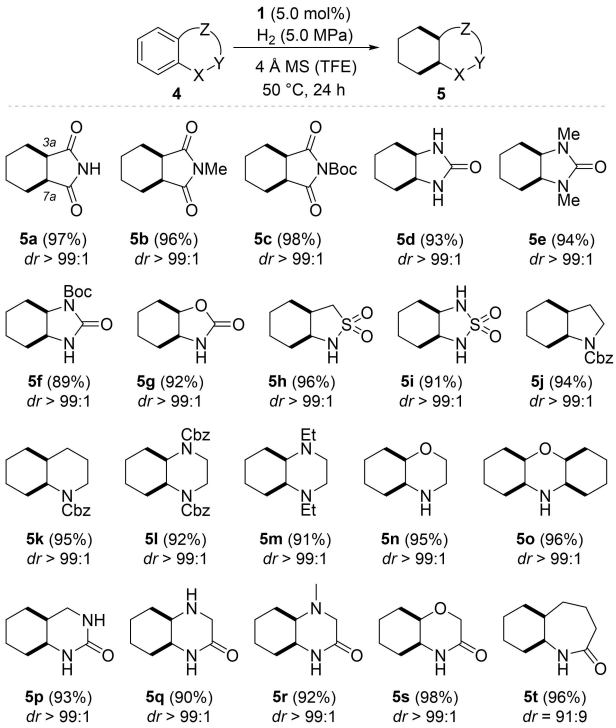
[a] The reactions were performed on a 0.10 mmol scale, low yields of **3a** correspond either to low conversion or to hydrodefluorination as major reaction pathway yielding **5a** as main product. cod = 1,5-cyclooctadiene, Dipp = 2,6-diisopropylphenyl.

[b] Conversion, yields and diastereomeric ratio (*dr*) were determined by GLC analysis using *n*-dodecane as the internal standard.

[c] 4 Å molecular sieves (MS) was added.

With the optimized conditions in hand, we began to test the limits of the catalyst towards an array of heterocycles (Scheme 2). We revisited different non-substituted benzo-fused heterocycles and succinimide **5a** was obtained in 97% yield as a single diastereoisomer, indicating that the two stereogenic centers at C3a and C7a of the octahydroisoindole core were established selectively. Their *cis* relationship was confirmed by comparison with spectroscopic data of authentic material.[13] The free amine as well as common protecting groups were well tolerated in 1*H*-indene-derived heterocycles.

Phthalimides (**4a–4c**), 2-benzimidazolones (**4d–4f**), 2-benzoxazolinone (**4g**), 1,3-dihydrobenzo[*c*]-isothiazole-2,2-dioxide (**4h**), 1,3-dihydro-2,1,3-benzothiadiazole-2,2-dioxide (**4i**) and indoline (**4j**) were easily converted to their saturated congeners in high yields with perfect selectivity (**5a–5j**, 89–98%, *dr* > 99:1). It should be noted, that the sulfone moiety within the substrates does not interfere with the arene reduction. The saturated heterocycles **5h** and **5i** were isolated in good yields and selectivities without notable catalyst poisoning nor undesired side reactions. To further expand the substrate scope of simple heterocycles, we subjected benzo-fused six-membered heteroarenes to our hydrogenation protocol. The saturated congeners of quinolone (**4k**), quinoxalines (**4l**, **4m**), 3,4-dihydro-2*H*-3,4-benzoxazine (**4n**), 3,4-dihydroqui-




**Scheme 2.** Scope and Diastereoselectivity of the Rhodium-Catalyzed Hydrogenation of Simple Benzo-fused *N*-Heterocycles. The reactions were performed on a 0.50 mmol scale. The diastereomeric ratio (*dr*) was determined by NMR analysis of the crude product mixture. Reported yields refer to isolated material after purification by flash column chromatography. Boc = *tert*-butoxycarbonyl. Compounds **5j**–**5l** were protected after hydrogenation to facilitate purification (Cbz = benzyloxycarbonyl).

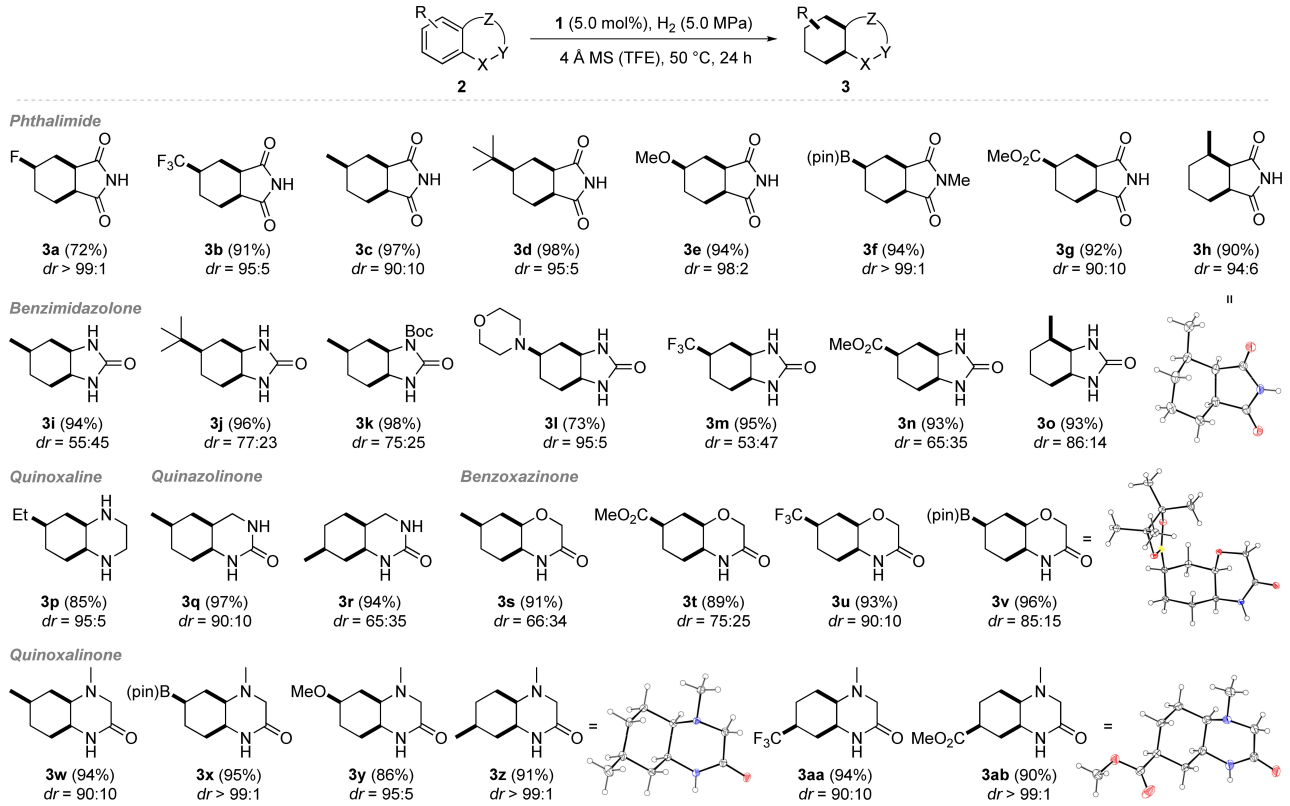
nazolin-2(1*H*)-one (**4p**), 3,4-dihydro-quinoxalin-2(1*H*)-ones (**4q**, **4r**) and 2*H*-benzo-[*b*][1,4]oxazin-3(4*H*)-one (**4s**) were obtained in high yields as single isomers (**5k**–**5n** and **5p**–**5s**, 90–98%, *dr* > 99:1). In all products, the two annulated rings were exclusively linked in a *cis* fashion. Moreover, phenoxazine (**4o**) bearing two aromatic entities and the highly flexible 1,3,4,5-tetrahydro-2*H*-benzo[*b*]azepin-2-one (**4t**) were selectively converted to the alicyclic products **5o** and **5t** in excellent yields with good selectivities (both 96%, *dr* > 99:1 and *dr* = 91:1). In all cases, the hydrogenation displayed consistent results regarding its chemoselectivity (yield) and diastereoselectivity (*dr*).

In a second set of experiments, the influence of substituents at the arene core in combination with the respective heterocycle was studied. Consequently, phthalimides bearing substituents at the C4 or C5 position were subjected to the optimized reaction conditions and they underwent the reduction towards the saturated product smoothly (**3a**–**3h**, 72–98%). The diastereomeric ratios were found to exceed 90:10 in all instances (Scheme 3). Moving on to the electronically different benzimidazolones, the yields remained high for most examples but the selectivity of the process significantly decreased (**3i**–**3o**, 73–98%, *dr* = 53:47 to *dr* = 95:5). The diastereomeric ratio dropped to a nearly even ratio when a relatively small methyl (**3i**) or trifluoromethyl (**3m**) substituent was attached to the reactive arene core. Larger substituents (**3j**, **3l**), a protection at a nitrogen atom (**3k**), or a closer proximity to the ring fusion (**3o**) increased the *dr* significantly providing the all-*cis* products in reasonable to good selectivities.

Encouraged by the broad scope of the hydrogenation reaction, we turned our attention to bicyclic, fused six-membered rings which display a more flexible backbone. 6-Ethyl quinoxaline (**2p**) was subjected to the reaction conditions and the saturated product **3p** was isolated in 85% yield with a high diastereomeric ratio favoring the all-*cis* product (*dr* = 95:5). In a similar regime, saturated 6- and 7-methyl quinazolinones were obtained in high yields employing the standard protocol (**3q** and **3r**, 94–97%). Noticeably, the 6-substituted quinazolinone **3q** was obtained with a significantly improved selectivity (*dr* = 90:10) compared to the 7-methyl quinazolinone **3r** (*dr* = 65:35). Subsequently, 6-substituted benzoxazinones were found to be compatible (**3s**–**3v**, 89–96%, *dr* = 66:34 to *dr* = 90:10) with the reaction conditions. Moreover, in the hydrogenation of 6- and 7-substituted *N*-methyl quinoxalinones the arenes were exclusively converted to the alicyclic all-*cis* products which were isolated in nearly quantitative yields and high selectivities (**3w**–**3ab**, 86–95%, *dr* = 90:10 to *dr* > 99:1).

In all cases, the robustness of the reaction was high and the reactivity of the arene ring was retained in the hydrogenation process although electron-donating or electron-withdrawing groups were present. An array of functional groups including amino (morpholine), fluoro, methyl, methoxy, methoxycarbonyl (ester), trifluoromethyl, *tert*-butyl groups as well as the valuable boronate entity were all well tolerated under these conditions. In every single product, the two annulated rings were exclusively linked in a *cis* fashion. Diastereomeric ratios refer to the position at a third stereogenic center which is linked to the respective substituent. Most functional groups resulted in high diastereoselectivites comparable or even better than alkyl substituents. The relative configuration of the saturated bicyclic products was corroborated by single-crystal X-ray diffraction of representative examples (products **3h**, **3v**, **3z**, and **3ab**) and unambiguously confirmed.[14] The higher flexibility, the different electronics of the heterocycles or substituent attached to the arene can be responsible for the observed reduced stereoselectivity.

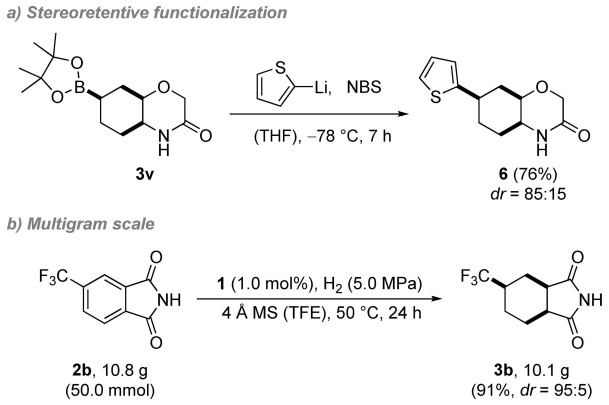
The easily accessible saturated heterocycles invited further studies regarding consecutive reactions. The high selectivity obtained in the hydrogenation of




**Scheme 3.** Scope and Diastereoselectivity of the Rhodium-Catalyzed Hydrogenation of Substituted Benzo-fused *N*-Heterocycles. The reactions were performed on a 0.50 mmol scale. The diastereomeric ratio (*dr*) was determined by NMR analysis of the crude product mixture. Reported yields refer to isolated materials (containing both diastereomers) after purification by flash column chromatography. Boc = *tert*-butoxycarbonyl, Pin = pinacolato. (See the SI for details).

boronate **3 v** enables the introduction of other functional entities at the 6-position of the heterocyclic carbon skeleton. For instance, the stereoretentive direct substitution of the boronate by carbon nucleophiles was accomplished. These transformations have become a reliable tool for the construction of stereogenic centers that bear exclusively carbon substituents.[15] It could be shown for boronate **3 v** that aryl lithium reagents such as 2-thienyllithium induced a clean substitution without compromising the *dr* and furnished product **6**, respectively. The Zweifel type olefination occurred stereospecifically,[16] the *dr* remained unaltered and allowed the incorporation of thiophene, a common motif in pharmaceuticals and agrochemicals (Scheme 4a, NBS = *N*-bromosuccinimide).[17]

Furthermore, the scalability of our protocol was exemplified by the hydrogenation of heterocycle **2 b** on a synthetically useful 50.0 mmol scale using only 1 mol% of **1**. The reaction provided multi-gram quantities of the saturated building block **3 b** in very good yields and high selectivity (Scheme 4b). In all experiments, the reaction mixture was a homogeneous solution at the beginning, but a rhodium precipitate was formed under reductive conditions. Previous




**Scheme 4.** Stereoretentive Substitution of Boronate **3 v** by 2-Thienyllithium to Furnish Product **6** and Multi-Gram Scale Reaction of Phthalimide **2 b**.

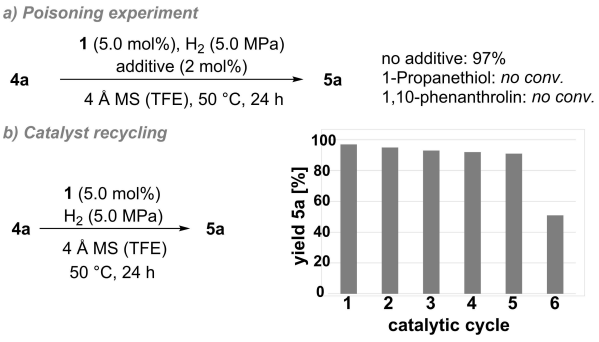
studies had revealed, that *in situ* formed small rhodium nanoparticles are the catalytically active species.[8b,9g,12] The nature of the active species was further validated through poisoning experiments.[18] It is assumed that heterogeneous catalysts have fewer active sites compared to single-site homogeneous catalysts, which in

turn is the reason why sub-catalytic additives can poison a heterogeneous catalyst. In our case, 1-propanethiol or 1,10-phenanthroline were found to have a detrimental effect on the hydrogenation reaction. Only 2 mol% of the respective additive were sufficient to suppress the activity of the heterogeneous catalyst (Scheme 5a). On the positive side, heterogenous catalysts lend themselves for recovery and can be re-used. With the rhodium precatalyst **1**, recycling experiments showed that the rhodium nanoparticles could be successfully separated and employed for a new catalytic run. Separation was achieved by centrifugation and the particles were used without modification in the subsequent run. As a result, the catalyst retained its activity in six consecutive catalytic cycles (97–51%, *dr* > 99:1). In the sixth catalytic experiment the yield of the hydrogenated product **5a** decreased significantly (Scheme 5b).

In summary, the rhodium-catalyzed chemo- and diastereoselective arene hydrogenation has been expanded to an array of *N*-heterocycles. The arene core of the respective heterocycle was selectively reduced, while two or three stereogenic centers were formed in a single operation with a predictable outcome. The functional group tolerance is extensive and the utility of the generated products is further increased by consecutive reactions, e.g. a stereospecific derivatization, which involved the incorporation of other chemically useful entities. The catalysis protocol shows potential for its application in the total synthesis of biologically relevant compounds.

## Experimental Section

**Hydrogenation of Benzo-fused *N*-Heterocycles**. Rhodium catalyst **1** (5.0 mol%), the respective heterocycle (0.5 mmol, 1.0 equiv.) and powdered 4 Å MS (50 mg) were filled in an oven-dried vial. TFE (0.2 M) was added and the reaction was pressurized and depressurized with hydrogen gas three times before the hydrogen pressure was set to 5.0 MPa. The reaction mixture was stirred at 50 °C for 24 h. Subsequently, the autoclave was carefully depressurized. The crude mixture was filtered over Celite® (eluent: dichloromethane) and evaporated to dryness. Then, the crude material was purified by flash column chromatography yielding the respective saturated heterocycle.




**Scheme 5.** Catalyst Poisoning Studies and Recycling Experiments of the Rhodium-Catalyzed Arene Hydrogenation.

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