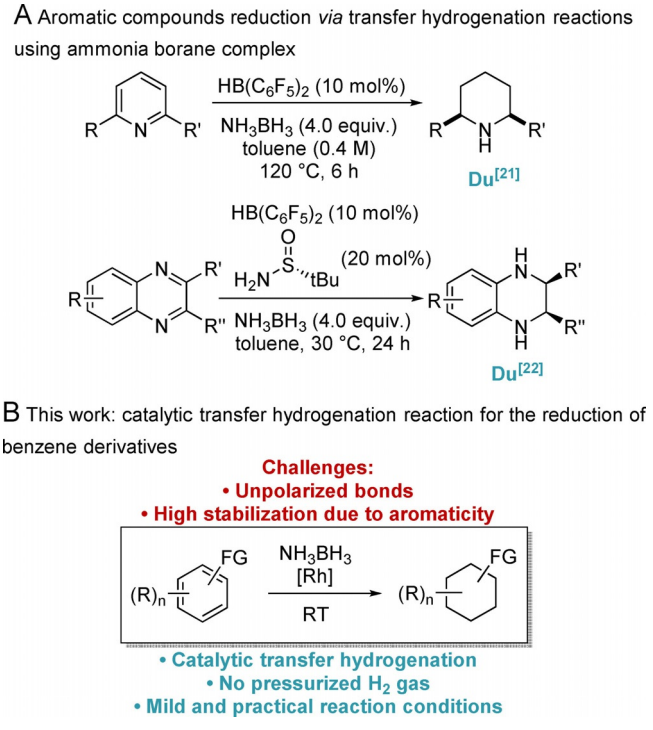
Rhodium Catalysis

Catalytic Transfer Hydrogenation of Arenes and Heteroarenes

Coralie Gelis, Arne Heusler, Zackaria Nairoukh, and Frank Glorius*[a]

Abstract: Transfer hydrogenation reactions are of great interest to reduce diverse molecules under mild reaction conditions. To date, this type of reaction has only been successfully applied to alkenes, alkynes and polarized unsaturated compounds such as ketones, imines, pyridines, etc. The reduction of benzene derivatives by transfer hydrogenation has never been described, which is likely due to the high energy barrier required to dearomatize these compounds. In this context, we have developed a catalytic transfer hydrogenation reaction for the reduction of benzene derivatives and heteroarenes to form complex 3-dimensional scaffolds bearing various functional groups at room temperature without needing compressed hydrogen gas.

Transfer hydrogenation reactions involve the transfer of hydrogen from a donor to an acceptor resulting in the oxidation of the donor and reduction of the acceptor.[1,2] Reduction of compounds by transfer hydrogenation presents many advantages, for instance pressurized hydrogen gas and the associated complicated reaction setup are not required. The first transfer hydrogenation reaction was described by Knoevenagel in 1903 using dimethyl 1,4-dihydro terephthalate as the donor and acceptor in the presence of palladium black.[3] Since this first report, many methods have been developed using different hydrogen sources and both homogeneous and heterogeneous catalysts.[1,2] Indeed, in many cases the homogeneous complex often transform into heterogeneous (nanoparticle) species during reactions and represent the active catalyst, which is convenient for the handling, separation and recycling of the catalyst.[4] Concerning hydrogen sources, isopropanol and formic acid are commonly used, but many others compounds can be employed, such as, Hantzsch esters, formate salts, amines, etc.[1,2] More recently, ammonia borane complex has received a lot of attention due to its stability, high hydrogen storage capacity (19.6 wt%) and ready availability. For these reasons, the reduction of diverse motifs such as ketones, imines, alkenes and alkynes has been studied using ammonia borane as the hydrogen donor.[5–20] Nevertheless, only two studies have been reported on the reduction of aromatic substrates (Scheme 1 A). First, Du and co-workers reported in 2016 the reduction of pyridines in the presence of borane as a catalyst.[21] The second example was published in 2017 by the same group, describing the transfer hydrogenation of quinoxalines catalyzed by a chiral frustrated Lewis pair.[22] The reduction of N-heterocycles was also described using other hydrogen donors, for example formic acid in the presence of cobalt nanoparticles as the catalyst.[23] Despite these advances, to the best of our knowledge the reduction of aromatic compounds via transfer hydrogenation is still limited to heteroarenes. Indeed, the reduction of benzene derivatives represents a significant challenge due to their strong aromatic stabilization (30–36 kcal mol^{-1}) (Scheme 1 B). Thus, the reduction of these compounds is often linked to the use of high hydrogen gas pressure and/or harsh reaction conditions. For these reasons, the development of transfer hydrogenation reaction to reduce benzene derivatives would provide an elegant alternative



Scheme 1. Transfer hydrogenation reactions.

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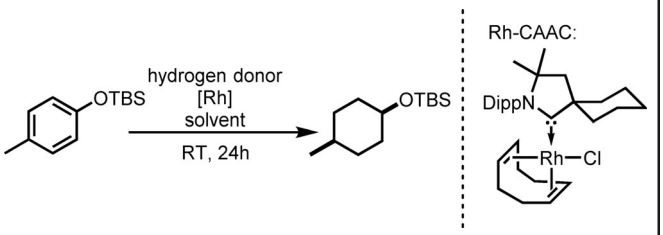
method to access diverse cyclohexanes under mild and convenient reaction conditions. Herein, we demonstrate that a rhodium catalyst in the presence of ammonia borane in trifluoroethanol can be used to promote the reduction of a broad variety of arenes and heteroarenes.

Based on our previous experience in selective high-pressure heterogeneous hydrogenation of fluoro-, silyl-, borylated-arenes and fluoropyridines[24–27] using the Bertrand-Zeng catalyst,[28,29] we envisioned that Rh-CAAC complexes could also be suitable catalyst precursors to develop a transfer hydrogenation reaction for the reduction of benzene derivatives. We began our investigation by assessing the activity of the Bertrand-Zeng catalyst in transfer hydrogenation reactions using ammonia borane. These preliminary results were encouraging and demonstrated the feasibility of the designed reaction (Table 1, entry 1). However, during these initial studies, simple and commercially available $[Rh(COD)Cl]_2$ was found to be better than Rh-CAAC (Table 1, entry 2). Interestingly, during the course of the reaction, the orange reaction mixture turned to a black suspension. This observation prompted us to examine the activity of different heterogeneous complexes. Rh/Al led to the formation of the desired product, albeit with lower diastereomeric ratio than $[Rh(COD)Cl]_2$. Other heterogeneous catalysts were not active (Table 1, entry 3 and cf. Table S3 in Supporting Information). Finally, different solvents and hydrogen donors were screened but only ammonia borane or a related amine borane derivative in TFE or HFIP were found to be reactive (Table 1, entries 4–9). To improve the reproducibility of the method, reaction condition-based sensitivity screening developed by the group was conducted (cf. Figure S7 in the Supporting Information).[30]

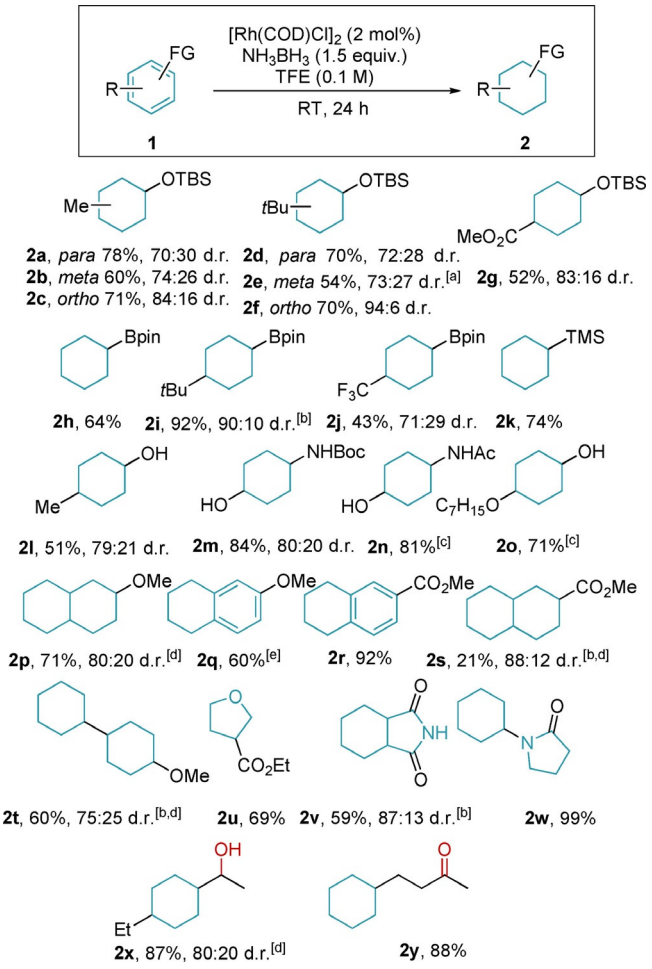
With the optimized conditions in hand, we then explored the scope of this transfer hydrogenation reaction (Scheme 2).

Table 1. Optimization.



Entry	Catalyst	Solvent[b]	Hydrogen donor[c]	Yield [%]	d.r.
1[a]	Rh-CAAC	TFE	NH_3BH_3	22	73:27
2	$[Rh(COD)Cl]_2$	TFE	NH_3BH_3	78	70:30
3[b]	Rh/Al_2O_3	TFE	NH_3BH_3	79	64:36
4[c]	$[Rh(COD)Cl]_2$	hexane	NH_3BH_3	0	–
5[c]	$[Rh(COD)Cl]_2$	THF	NH_3BH_3	0	–
6[c]	$[Rh(COD)Cl]_2$	EtOH	NH_3BH_3	0	–
7[c]	$[Rh(COD)Cl]_2$	HFIP	NH_3BH_3	64	70:30
8	$[Rh(COD)Cl]_2$	TFE	$THF{\cdot}BH_3$	0	–
9	$[Rh(COD)Cl]_2$	TFE	pinacolborane	19	65:35

General conditions: hydrogen donor (1.5 equiv), dilution (0.1 M), catalyst loading (2 mol%). [a] 50 °C, hydrogen donor (1.0 equiv). [b] 50 °C, overnight, hydrogen donor (1.0 equiv). [c] Reaction time: overnight. CAAC = cyclic alkyl amino carbene; COD = 1,5-cyclooctadiene; TFE = 2,2,2-trifluoroethanol; HFIP = hexafluoroisopropanol.



Scheme 2. Scope of the transfer hydrogenation of arenes. All data are reported as isolated yields. d.r. values are determined by GC or ^{1}H NMR. a) Reaction time of 48 h. b) Reaction performed at 50 °C. c) Undetermined diastereomeric ratio because of complex mixture. d) 2 equivalent of ammonia borane were used. e) 1 equivalent of ammonia borane was used. f) 2.5 equivalent of ammonia borane were used. g) 3 mol% of catalyst were used.

It was first shown that disubstitution on benzene rings in *ortho*-, *meta*- and *para*-positions is well tolerated and afforded the corresponding cyclohexanes (**2a** to **2c**) with good results. The major isomer of (**2a**) was shown to be *cis* by comparison of the ^{1}H NMR spectra with the known literature data.[31] The reaction proceeded smoothly even with more sterically hindered substrates (**2d** to **2f**). A slight increase of the diastereomeric ratio was observed for the substrates with *ortho*-substituents (**2c** and **2f**). The functional group tolerance of this method was then studied. The introduction of ester, borylated and silylated groups was tolerated and led to the formation of the products **2g** to **2k**. Pleasingly, a series of cyclohexanols (**2l** to **2o**) was also synthesized with this methodology. It is noteworthy that the major isomer obtained for (**2l**) and (**2m**) was the *trans*. The Beller group recently reported similar results and explained this *trans*-selectivity by the formation of the thermodynamically more stable isomer.[32] Protected amines were also well tolerated leading, among others, to the formation of [H6]-analog of paracetamol (**2n**). To further demonstrate the scope

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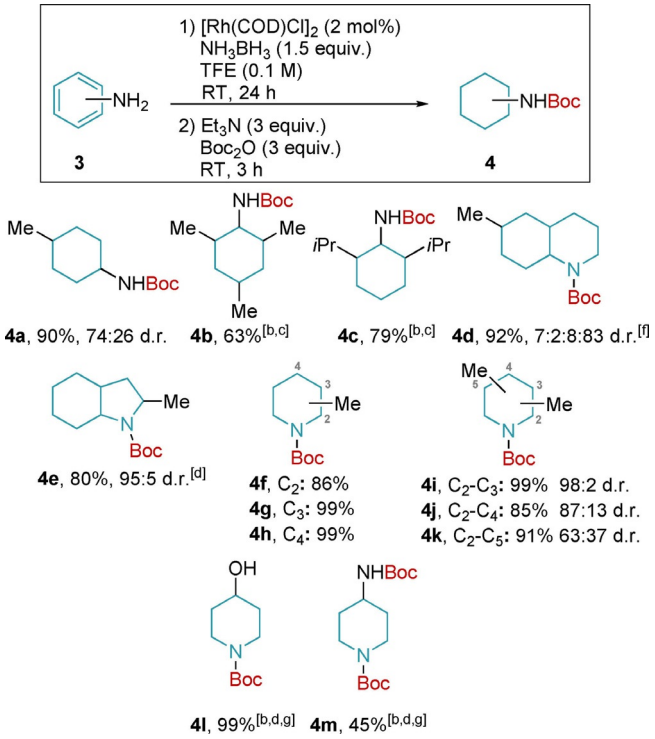
of this transfer hydrogenation reaction, naphthalene derivatives were examined and pleasingly, by changing the quantity of ammonia borane, we were able to regioselectively form the product (**2q**) or the fully reduced product (**2p**). The same selectivity was observed when using a naphthalene derivative bearing an electron-withdrawing group. However, unfortunately in this case the completely reduced product (**2s**) was obtained in only 21% yield which is likely due to a lower affinity of the catalyst for this electron poor substrate (**2s** vs. **2p**). Next, the reduction of a biaryl (**1t**) was studied. In this case, only the fully reduced product (**2t**) could be obtained when using 2 equivalents of ammonia borane at 50 °C. Lowering the quantity of ammonia borane led to a mixture of the [H12]-product and the two regioisomers of the [H6]-adduct. The reduction of heteroaromatic compounds was also shown to be possible with the formation of products **2u** to **2w**. Finally, in order to gain some insight into the chemoselectivity of the reaction, we studied the hydrogenation of aromatic ketones. When the ketone is directly conjugated with the aromatic ring, the latter was completely reduced to form the alcohol (**2x**). However, when the ketone is not conjugated, only selective reduction of the aromatic ring was observed, as shown with the formation of product **2y**.

Next, the reduction of aromatic rings bearing free amines followed by their protection in situ was examined (Scheme 3). This protocol permitted *N*-Boc protected cyclohexanes (**4a** to **4c**) to be formed in good yields. Notably, highly substituted compounds (**4b**) and (**4c**) (up to 4 substituents) were formed in very good yields, albeit as complex mixture of diastereoisomers. Quinoline (**3d**), indole (**3e**) and pyridines (**3f** to **3m**) were also successfully reduced by this transfer hydrogenation reaction and converted into their corresponding saturated products in excellent yields.



Scheme 3. Scope of the transfer hydrogenation of arenes bearing free amines. All data are reported as isolated yields. d.r. values are determined by GC or ^{1}H NMR. a) Reaction time of 48 h. b) Reaction performed at 50 °C. c) Undetermined diastereomeric ratio because of complex mixture. d) 2 equivalent of ammonia borane were used. e) 1.0 equivalents of ammonia borane was used. f) 2.5 equivalents of ammonia borane were used. g) 3 mol% of catalyst were used.

Most notably, this procedure enables the facile reduction of various arenes including valuable silyl-, trifluoromethyl- and borylated-arenes, which was recently reported using 50 bar of hydrogen gas.[25,26,33] To gain a better understanding of the reaction mechanism, different experiments were conducted. First, average deuterium incorporation in the product was studied using different deuterated ammonia boranes and trifluoroethanols (cf. Table S7 in the Supporting Information).[34] The results seem to indicate that the protic hydrogen from the solvent and the hydridic hydrogen from borane are primarily involved in the hydrogen transfer. These results are consistent with the fact that trimethylamine borane can also be used instead of ammonia borane to promote transfer hydrogenation (as shown during the optimization (cf. Table S6 in the Supporting Information)). The dehydrogenation and the hydrogenation processes were also studied. First, the ability of the catalyst to promote dehydrogenation of ammonia borane was examined by monitoring the formation of H_2 gas under different reaction conditions (cf. Figure S1 in the Supporting Information). Only slow gas evolution was observed in the absence of the rhodium catalyst, which is indicative of the catalysts important role in the dehydrogenation process. A control experiment also demonstrated the importance of the catalyst in the reduction step. Then, reactions employing hydrogen gas with or without ammonia borane were performed (Scheme 4A). When using 1 bar of hydrogen gas without ammonia borane, no conversion of the starting material into the cyclohexane derivative was observed. When increasing the pressure to 2 bar, the formation of reduced products **5a** and **6a** was observed. These deprotected products were never observed when using ammonia borane, which indicates that either the active catalyst formed or the mechanism pathway is different. Preformation of the active catalyst in the presence of ammonia borane followed by the addition of the substrate and hydrogen gas led to the formation of the product in only 8% yield, which could be due to residual undegraded ammonia borane. No product was formed when the catalyst preformation time was increased to 24 h (cf. Figure S2 in the Supporting Information). This indicates the crucial role of the ammonia borane in both the formation of the active catalyst and the reduction of the arene. Next, the reaction was performed under 1 bar of deuterium gas in the presence of ammonia borane (Scheme 4B). After 1 h at room temperature, the formation of the reduced product was observed with no deuterium incorporation. After 2 h, only a low deuterium incorporation in the product was measured. After 24 h of reaction, 50% average deuteration on all the position of the product was observed. These experiments seem to indicate that under the described reaction conditions, the reduction of the arene could be due to a direct hydrogen transfer and indirect via the equilibrium described in

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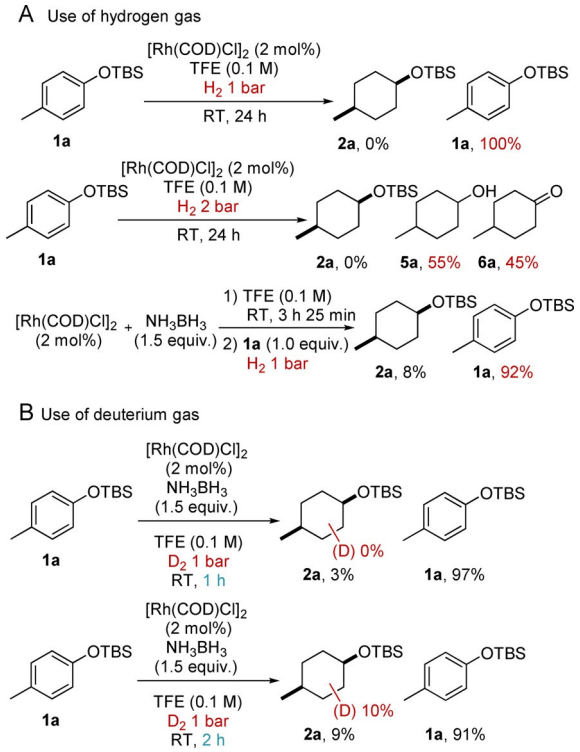

Scheme 4. Mechanistic studies.

the Supporting Information S3 leading to the formation of hydrogen gas that can also be transferred to the arene. A deuterium exchange between deuterium gas and ammonia borane could lead to underestimated deuterium incorporation which could indicate a favored indirect transfer hydrogenation mechanism. Finally, to clarify the nature of the active catalyst, different experiments were conducted which indicated that the formed rhodium nanoparticles could be the active catalyst in this transformation (cf. Figures S4–S6 in the Supporting Information).

Overall, this work describes the catalytic transfer hydrogenation of benzenoid arenes via a dual mechanism including direct and indirect hydrogen transfer. Furthermore, this method provides direct access to various cyclohexane derivatives and saturated heterocycles, difficult to prepare by other methods, without the need of syngas and the associated complicated reaction setup or harsh reaction conditions.

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Conflict of interest

The authors declare no conflict of interest.

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