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Letter

trans-Selective and Switchable Arene Hydrogenation of Phenol Derivatives

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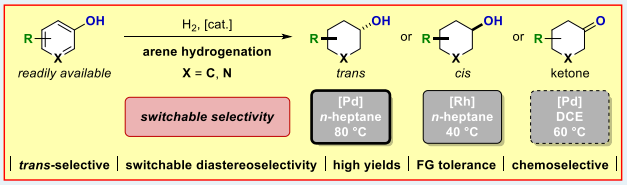
ABSTRACT: A *trans*-selective arene hydrogenation of abundant phenol derivatives catalyzed by a commercially available heterogeneous palladium catalyst is reported. The described method tolerates a variety of functional groups and provides access to a broad scope of *trans*-configurated cyclohexanols as potential building blocks for life sciences and beyond in a one-step procedure. The transformation is strategically important because arene hydrogenation preferentially delivers the opposite *cis*-isomers. The diastereoselectivity of the phenol hydrogenation can be switched to the *cis*-isomers by employing rhodium-based catalysts. Moreover, a protocol for the chemoselective hydrogenation of phenols to cyclohexanones was developed.



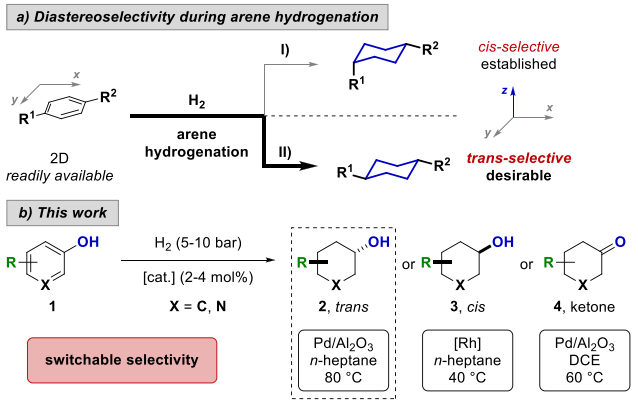
KEYWORDS: *arene hydrogenation, trans-selective, switchability, cyclohexanols, palladium catalysis*

Arene hydrogenation is a powerful tool to transform simple, two-dimensional precursors into more complex, three-dimensional scaffolds.[1] A plethora of readily available arenes and heteroarenes provided by established transformations (e.g., cross-coupling, aromatic substitution), offer potential access to a wide array of cyclic saturated motifs. The strategic importance of arene hydrogenation is exemplified by the industrial synthesis of cyclohexane[2] and cyclohexene[3] from benzene on multi-ton scale.

The field of arene hydrogenation has constantly evolved over the last several decades, and progress toward the stereo- and chemoselective hydrogenation of (hetero)aromatic compounds has been achieved. Chemoselective hydrogenation of arenes provides direct access to saturated carbo- and heterocycles containing reductively labile functional groups directly attached to the reactive center.[1d,4] The competing hydrodefunctionalization pathway observed for fluorinated,[4a−c] borylated[4d,e] or silylated[4f] arenes can be limited by the choice of suitable reaction conditions. Additionally, the enantioselective hydrogenation of heteroarenes provides rapid access to chiral, saturated heterocycles through the controlled formation of stereocenters.[5]

During the (chemoselective) hydrogenation of multisubstituted aromatic compounds, multiple stereocenters are formed in one step allowing for the formation of several product diastereomers. In general, the transition-metal catalyzed hydrogenation of arenes favors the corresponding all-*cis* configuration of the saturated analogues (Scheme 1a, path I).[1,4] The *cis*-selectivity results from a fast, continuous hydrogenation of the substrate through a non-interrupted coordination to the catalyst. The corresponding *trans*-isomers require a π-facial exchange of the dearomatized diene or olefin intermediate via substrate desorption and readsorption to the catalyst, which is associated with binding to the sterically more hindered π-face. For this reason, the corresponding *trans*-isomers remain minor side products during arene hydrogenation.[1,4] However, *trans*-isomers of multisubstituted saturated carbo- and heterocycles are desirable product motifs, and their synthesis starting from the corresponding *cis*-isomers is

Scheme 1. Diastereoselectivity in the Process of Arene Hydrogenation and Switchable (Stereo)selectivity in the Hydrogenation of Phenols



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often limited, rendering a direct *trans*-selective hydrogenation of arenes desirable (Scheme 1a, path II).

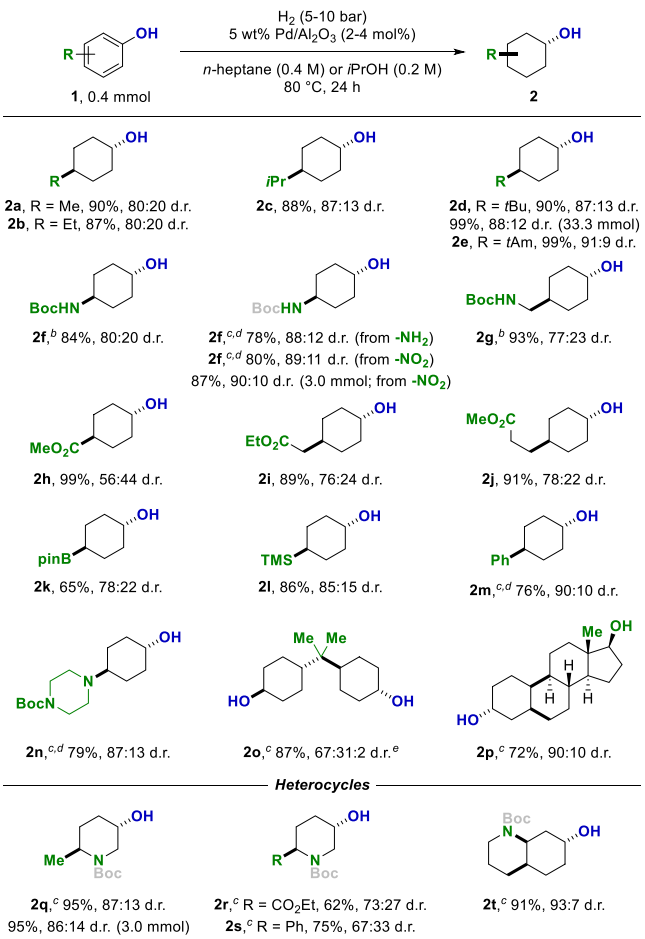
Encouraged by a few rare examples with diminished *cis*-selectivity during our previous studies on the rhodium cyclic (alkyl)(amino)carbene (Rh−CAAC)-catalyzed chemoselective hydrogenation of arenes,[4] we sought to investigate the underexplored and limited *trans*-selective hydrogenation of arenes.[6] Especially unprotected phenols gave a relatively high ratio of the "undesired" *trans*-diastereomer in our previous rhodium-catalyzed studies. The hydrogenation of phenol is an important industrial process for the synthesis of cyclohexanone and cyclohexanols as the intermediates for Nylon-6 and 66.[2,7] Substituted cyclohexanols are also extensively used as valuable chemical feedstock and synthetic intermediates in the pharmaceutical, petrochemical, and fine chemical industry. Moreover, the resulting hydroxyl group provides a diverse synthetic handle for further functionalization of the products.

Herein, we report the first comprehensive study toward a *trans*-selective hydrogenation of arenes. *trans*-Cyclohexanols are synthesized from abundant phenols in a one-step reaction that tolerates a variety of functional groups (Scheme 1b).

We commenced our studies by investigating different transition-metal based catalysts in the hydrogenation of *p*-cresol. When switching from rhodium-based catalysts to heterogeneous palladium catalysts, we noticed an inversion in the diastereoselectivity of the reaction. Investigating the efficacy of different palladium catalysts in the reaction revealed that a 5 wt % Pd/Al_2O_3 system had the best selectivity toward the desired *trans*-cyclohexanol product, accompanied by only trace amounts of the unwanted cyclohexanone intermediate. After optimization, employing commercially available 5 wt % Pd/Al_2O_3 in *n*-heptane as the solvent, under a low hydrogen pressure of 5 bar at 80 °C provided the best *trans*-diastereoselectivity, yield, and chemoselectivity of the reaction. Hydrogenation of *p*-cresol furnished 4-methylcyclohexanol **2a** in 90% yield and 80:20 diastereomeric ratio (d.r., *trans*:*cis*).[8] To evaluate the sensitivity of our developed protocol, we conducted a reaction-condition-based sensitivity screen.[9] The influence on yield and diastereoselectivity was investigated by systematic variation of key reaction parameters (see Supporting Information).

With the optimized conditions in hand, we began investigating the scope of the reaction (Scheme 2). The hydrogenation of phenols bearing aliphatic substituents (**2a**−**e**) provided the corresponding *trans*-cyclohexanols in high yields. With increasing steric bulk in *para*-position, the diastereomeric ratio increased from 80:20 d.r. to 91:9 d.r. In addition, 4-*tert*-butylcyclohexanol **2d** was obtained in quantitative yield and 88:12 d.r. after scale-up to 5.0 g scale (33.3 mmol). Boc-protected *p*-aminophenol was hydrogenated to protected 4-aminocyclohexanol (**2f**) in 84% yield and 80:20 d.r. By switching the solvent from *n*-heptane to polar isopropanol and adding K_2CO_3 as base, the unprotected *p*-aminophenol could be hydrogenated to **2f** in high yield and with an increased diastereoselectivity of 88:12. Boc-protected *trans*-4-aminocyclohexanol could also be obtained after hydrogenation and protection of *p*-nitrophenol while reducing the nitro group and arene in a one-step procedure. Moreover, different ester substituents were tolerated furnishing *trans*-cyclohexanols with protected acids (**2h**−**j**). Aryl boronic acid derivative **1k** was hydrogenated giving access to the synthetically valuable *trans*-configurated organoboron compound **2k**. Additionally the organosilicon analogue **2l** could be obtained

Scheme 2. Substrate Scope for the *trans*-Selective Hydrogenation of Phenols[a]



[a]Combined yields of isolated product after column chromatography are given. The d.r. values were determined by GC-MS or ^{1}H NMR analysis prior to purification. Piperidines and amines were trapped with Boc_2O prior to isolation. For details, see Supporting Information. [b]48 h. [c]*i*PrOH as solvent. [d]K_2CO_3 as additive. [e]The ratio is *trans*/*trans*:*trans*/*cis*:*cis*/*cis*.

in 86% yield and 85:15 d.r. Chemoselective hydrogenation of the more substituted phenol ring compared to the phenyl substituent in *p*-phenylphenol delivered **2m** in 76% yield and 90:10 d.r. Additionally, a Boc-protected piperazine substituent was tolerated, giving the *trans*-configurated building block **2n** with two orthogonal sites available for further functionalization. The hydrogenation of bisphenol A, a common precursor for polycarbonates, provided compound **2o** bearing two *trans*-configurated cyclohexanols as the major isomer. Showcased by products **2a**−**2o**, a wide array of achiral building blocks with potential applications in pharmaceutical sciences could be synthesized. Moreover, the female sex hormone estradiol could be transformed into the corresponding saturated analogue **2p** in 72% combined yield and 90:10 d.r.

Since saturated heterocycles are an important structural motif, we extended the scope of the *trans*-selective hydrogenation to different heteroarenes (**2q**−**t**). By switching to isopropanol as polar solvent, poisoning of the palladium catalyst could be prevented.[10,1h] Hydroxypyridine **1q** was hydrogenated to the corresponding piperidine in 95% yield and 87:13 d.r. The reactivity and selectivity were preserved

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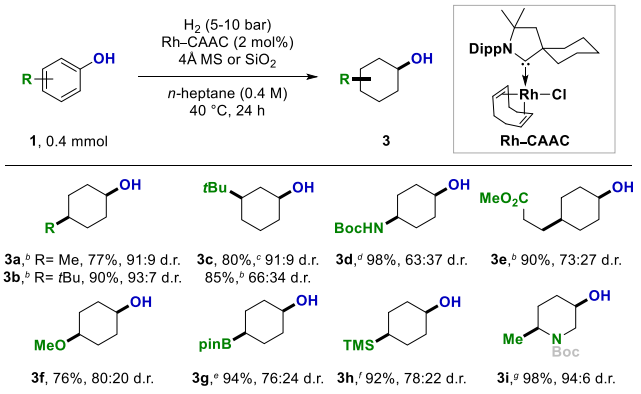
after scale-up of the developed method to 3 mmol. Reductively labile groups like esters (**2r**) and phenyl substituents (**2s**) were tolerated, enabling a *trans*- and chemoselective hydrogenation of pyridines. Additionally, quinoline derivative **1t** was *trans*-selectively hydrogenated, furnishing the perhydro product in 91% yield and 93:7 diastereomeric ratio. In almost all cases, the major diastereomer could be separated by column chromatography, providing access to the diastereomerically pure *trans*-configurated (heterocyclic) cyclohexanol derivatives with a broad variety of functional groups. The *trans*-selectivity of the hydrogenation was confirmed by X-ray diffraction analysis of products **2f**, **2m**, **2o**, and **2q**. Furthermore, the configuration of the majority of products were confirmed by NMR analysis.[8]

In many cases both product diastereomers of a newly developed method are of synthetic interest. However, switching the diastereoselectivity of established and newly developed protocols often remains non-trivial, and long synthetic routes are necessary. The *cis*-selective hydrogenation of phenols is frequently limited by poor functional group tolerance and cleavage of the carbon−oxygen bond by hydrogenolysis when employing standard heterogeneous catalysts (e.g., Rh/C, Rh/Al_2O_3) or $[Rh(COD)Cl]_2$ in combination with various catalyst supports.[11,6d] When using Rh−CAAC as a precatalyst[12] and 4 Å molecular sieves or silica gel as catalyst support, we could switch the diastereoselectivity to the corresponding *cis*-diastereomers without the undesired hydrogenolysis (Scheme 3).

Scheme 3. Substrate Scope for the *cis*-Selective Hydrogenation of Phenols[a]

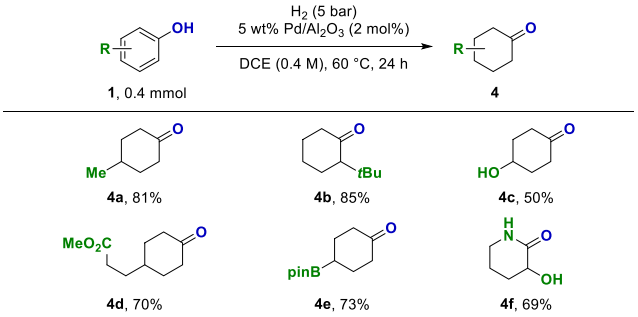


[a]Combined yields of isolated product after column chromatography are given. The d.r. values were determined by GC-MS or ^{1}H NMR analysis prior to purification. Piperidines were trapped with Boc_2O prior to isolation. For details, see Supporting Information. CAAC = cyclic (alkyl)(amino)carbene. Dipp = 2,6-diisopropylphenyl. [b]$[Rh(COD)Cl]_2$ (2 mol %). [c]5 wt % Pd/Al_2O_3 (4 mol %). [d]48 h. [e]H_2 (50 bar). [f]H_2 (20 bar). [g]*i*PrOH as solvent.

Phenols with simple alkyl chains could be hydrogenated using $[Rh(COD)Cl]_2$ as a catalyst. The hydrogenation of *p*-cresol and *p*-*tert*-butylphenol provided the corresponding cyclohexanols **3a** and **3b** in high yields and diastereoselectivities. *m*-*tert*-Butylphenol was hydrogenated and 3-*tert*-butylcyclohexanol **3c** was obtained in 85% yield and 66:34 d.r. (*cis*:*trans*) when using $[Rh(COD)Cl]_2$ as a catalyst. The diastereoselectivity of the reaction could be increased to 91:9 d.r. when using palladium on alumina instead. For phenols decorated with more labile functional groups, the Rh−CAAC system was used. Boc-protected *cis*-4-aminocyclohexanol **3d** and cyclohexanol **3e** with an ester substituent were obtained in excellent yields. Moreover, ether (**3f**), organoboron (**3g**), and organosilicon (**3h**) functionalities were well tolerated, rendering *cis*-configurated cyclohexanols with various functional groups accessible. The *cis*-selective hydrogenation protocol could be extended to pyridines, demonstrated by the hydrogenation of hydroxypyridine **2i**. When using $[Rh(COD)Cl]_2$ as the catalyst undesired hydrogenolysis of functional groups was observed. For example, cleavage of the carbon−oxygen bond (**3f**), carbon−silicon bond (**3h**), and hydrodeborylation (**3g**) could be detected (see Supporting Information for more details).

The chemoselective hydrogenation of phenols to cyclohexanones has been focus of different studies.[13,4g] The major challenge associated with chemoselective phenol hydrogenation is preventing the over-reduction of the reductively more labile carbonyl group. Herein, we present a simple variation of our protocol by using the same, commercially available 5 wt % Pd/Al_2O_3 as catalyst, 5 bar of hydrogen, and 1,2-dichloroethane (DCE) as solvent to target this challenge (Scheme 4). Hydrogenation of *p*-cresol and *o*-*tert*-butylphenol in DCE provided 4-methylcyclohexanone **4a** in 81% yield and 2-*tert*-butylcyclohexanone **4b** in 85% yield.

Scheme 4. Substrate Scope for the Ketone-Selective Hydrogenation of Phenols[a]



[a]Yields of isolated product after column chromatography are given. DCE = 1,2-dichloroethane.

During the hydrogenation of hydroquinone, reduction of one carbonyl group of the diketo intermediate was observed, and 4-hydroxycyclohexanone **4c** was obtained as the major product in 50% yield. Reductively labile groups like esters (**4d**) and pinacol boronic esters (**4e**) were tolerated, and the cyclohexanone derivatives were obtained in 70% and 73% yield, respectively. The major side products during the chemoselective hydrogenation of phenols to cyclohexanones were the corresponding cyclohexanols (see Supporting Information).

Having established three valuable protocols for the diastereo- and chemoselective hydrogenation of phenols, we sought to investigate the influence of the substitution pattern on reactivity and diastereoselectivity (Scheme 5). During the palladium-catalyzed hydrogenation of *p*-cresol, the thermodynamically more stable *trans*-4-methylcyclohexanol **2a** was obtained as the major diastereomer. When employing a rhodium-based catalyst, the diastereoselectivity was inverted to the thermodynamically less stable *cis*-4-methylcyclohexanol **3a**. When changing the substrate from *p*-cresol to *m*-cresol, *cis*-3-methylcyclohexanol **3ab** was obtained as the major product for both catalytic systems (Pd and Rh). The same selectivity was

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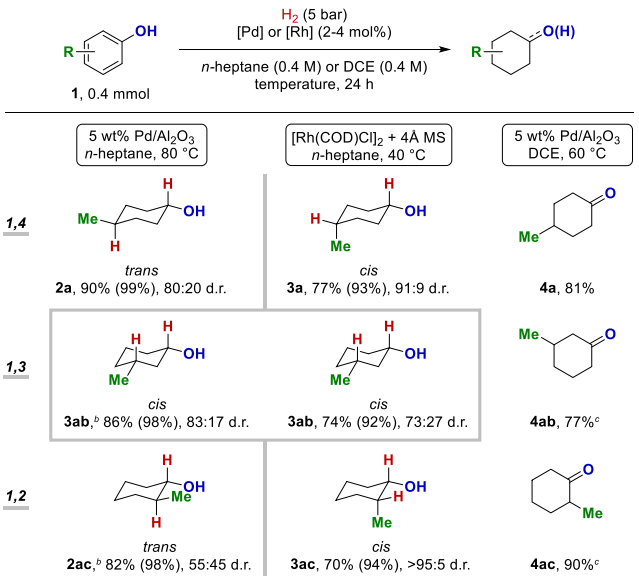
Scheme 5. Substitution Pattern and Diastereoselectivity for the Hydrogenation of Phenols[a]



[a]Combined yields of isolated product after column chromatography are given. Diastereoselectivity and yields in parentheses were determined by ^{1}H NMR analysis. For details, see Supporting Information. [b]H_2 (10 bar). [c]Yield determined by GC-FID analysis.

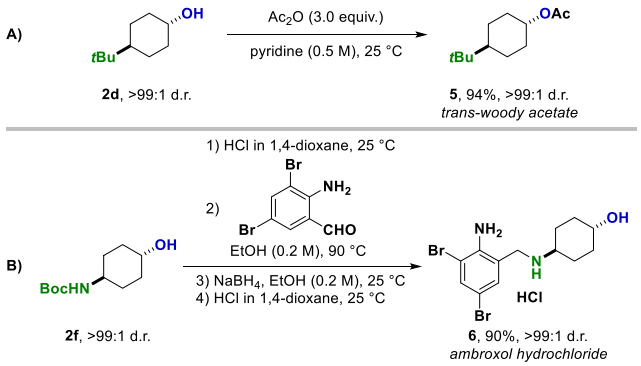
previously observed in the hydrogenation of *m-tert*-butylphenol (Scheme 3). The use of palladium on alumina as the catalyst furnished a higher ratio of the thermodynamically more stable *cis*-diastereomer in the case of 1,3-disubsituted cycloalkanes. The palladium-catalyzed hydrogenation of *o*-cresol provided *trans*-2-cyclohexanol **2ac** with low diastereoselectivity (55:45 d.r.), although *trans*-1,2-disubstituted cycloalkanes are thermodynamically favored. When employing the rhodium-based catalytic system, an excellent diastereoselectivity of >95:5 d.r. for *cis*-2-methylcyclohexanol **3ac** was observed. The chemoselective hydrogenation of phenols to cyclohexanones showed no significant influence caused by the substitution pattern, giving access to the volatile methylcyclohexanones **4a**−**4ac** in good yields. The catalytic system based on rhodium provides products generated by the all-*cis* addition[1,4] of hydrogen atoms to the substrates, whereas the catalytic system based on palladium gives access to the thermodynamically more stable diastereomers.

The proposed mechanism for the heterogeneous hydrogenation of phenols to cyclohexanols involves partially hydrogenated cyclohexenols (enol-forms) and the corresponding cyclohexanones (keto−enol tautomerism).[14] The *trans*-isomers are believed to be formed through desorption and readsorption of intermediate cyclohexanone/cyclohexenol species (π-facial exchange) followed by the *cis*-addition of hydrogen to enol intermediates.[1d,15]

Mechanistic experiments showed a fast consumption of the starting material and formation of 4-*tert*-butylcyclohexanone as an intermediate (see Supporting Information for more details). However, direct hydrogenation of 4-*tert*-butylcyclohexanone resulted in reduced diastereoselectivity (67:33 d.r.), compared with the hydrogenation of *p-tert*-butylphenol (87:13 d.r.). Hydrogenation of "diene" intermediates (e.g., 4-*tert*-butylcyclohex-2-en-1-one and 4-*tert*-butylcyclohex-3-en-1-one) resulted in roughly the same diastereoselectivity as the direct hydrogenation of *p-tert*-butylphenol. Diene intermediates could never be observed because of the fast hydrogenation of alkene double bonds. Key to the increased *trans*-selectivity during phenol hydrogenation could be the low concentration of the cyclohexanone intermediate, which disfavors the slow, direct ketone hydrogenation, forming the minor *cis*-isomer. The *trans*-isomer could be formed through a desorption and readsorption process of diene and enol intermediates, which is facilitated through keto−enol tautomerism. Deuteration studies show deuterium scrambling at the 2-position, supporting the rapid interconversion of keto and enol intermediates on the catalyst surface. In addition, increasing steric bulk in 4-position as well as the high reaction temperature favor the process of desorption and readsorption (π-facial exchange) and therefore increase the ratio of *trans*-products. Moreover, diastereomerically pure *trans*- and *cis*-4-*tert*-butylcyclohexanols (>99:1 d.r.) were subjected to the standard conditions, and no isomerization was observed, excluding a thermodynamically driven isomerization process.

Having established an efficient and versatile method for the *trans*-selective hydrogenation of phenols, we sought to demonstrate the synthetic utility of the obtained products (Scheme 6). Acetylation of *trans*-4-*tert*-butylcyclohexanol **2d**

Scheme 6. Synthetic Applications of *trans*-Cyclohexanols[a]



[a]For experimental details, see Supporting Information.

provided the *trans*-isomer of woody acetate **5**, a fragrance ingredient used in cosmetics.[16] Furthermore, ambroxol, a mucolytic agent used in the treatment of respiratory diseases, was synthesized.[17] Starting from inexpensive *p*-nitrophenol, Boc-protected *trans*-4-aminocyclohexanol **2f** was obtained in 87% yield and 90:10 d.r. on a 3 mmol scale in one step (Scheme 2). After separation of the diastereomers on silica gel, treatment of **2f** with HCl in 1,4-dioxane provided diastereomerically pure 4-*trans*-aminocyclohexanol. Imine formation with 2-amino-3,5-dibromobenzaldehyde, followed by $NaBH_4$ reduction and treatment with HCl gave access to ambroxol hydrochloride in 90% yield over four steps (Scheme 6B).

In conclusion, we have developed three sets of reaction conditions for the hydrogenation of abundant phenols providing access to either *trans*- or *cis*-configurated cyclohexanols, as well as cyclohexanones. The *trans*-selective hydrogenation of phenols is catalyzed by heterogeneous palladium on alumina and tolerates a variety of functional groups, giving access to building blocks with the opposite diastereoselectivity preferentially generated through the hydrogenation of arenes. The diastereoselectivity was inverted by employing rhodium-based catalysts and a simple and practical

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method for the chemoselective hydrogenation of phenols to cyclohexanones was established.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c03423.

Materials and methods, optimization of reaction condition, experimental procedure and characterization data for products, and synthesis procedure and characterization (PDF)

X-ray diffraction data (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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