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Letter

Synthesis of Tetrahydroquinolines via Borrowing Hydrogen Methodology Using a Manganese PN^3 Pincer Catalyst

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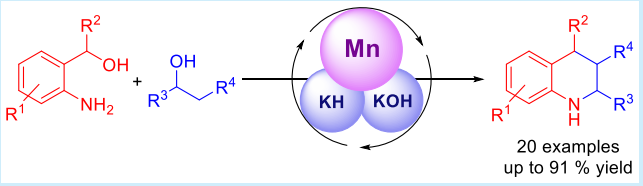
ABSTRACT: A straightforward and selective synthesis of 1,2,3,4-tetrahydroquinolines starting from 2-aminobenzyl alcohols and simple secondary alcohols is reported. This one-pot cascade reaction is based on the borrowing hydrogen methodology promoted by a manganese(I) PN^3 pincer complex. The reaction selectively leads to 1,2,3,4-tetrahydroquinolines thanks to a targeted choice of base. This strategy provides an atom-efficient pathway with water as the only byproduct. In addition, no further reducing agents are required.

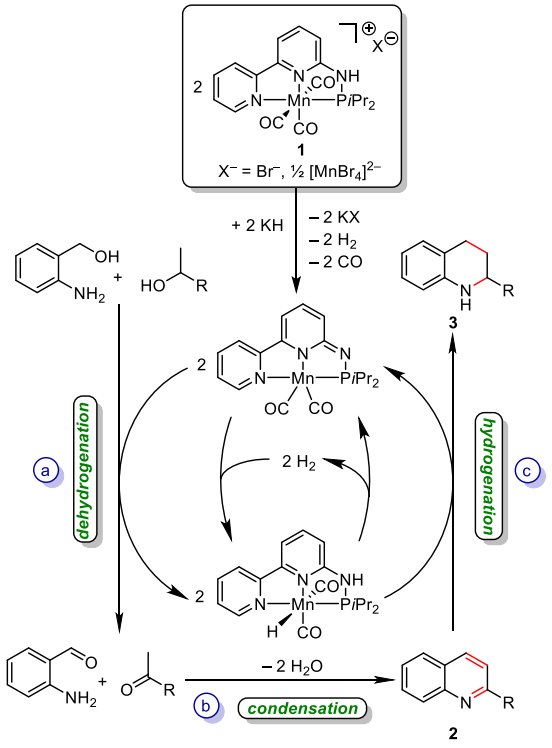


Nitrogen-containing heterocycles are indispensable substructures of important pharmaceuticals and agrochemicals.[1] Within this important substance class, the 1,2,3,4-tetrahydroquinoline[2] scaffold represents a particularly relevant building block for various natural products and pharmacologic active substances. While a number of synthetic approaches to tetrahydroquinolines exist,[2] the development of new catalytic processes that provide a faster and more (atom-) efficient access are highly desirable to reach the goals of a sustainable development.[3] The borrowing hydrogen (BH) methodology[4] offers an atom-economical pathway for the formation of carbon−carbon and carbon−nitrogen bonds utilizing inexpensive, abundant, and renewable starting materials.[5] Key to many BH processes is the catalytic acceptorless dehydrogenation[6,7] of an alcohol to form a carbonyl compound that can subsequently undergo further transformations, such as imine formation or aldol condensation. Finally, the catalyst returns the hydrogen to the condensation product to complete the BH cycle. While most catalyst systems have relied on precious metals, such as Ru and Ir,[4c] more abundant and less expensive base metal catalysts, including Mn, Fe, Co, and Ni, have received significant attention recently.[4d,7,8]

The BH methodology offers a simple opportunity to construct tetrahydroquinolines in an atom- and step-economical manner starting from 2-aminobenzyl alcohols and a second alcohol (Scheme 1, steps a−c) with water as the only byproduct.

However, previous attempts in the condensation of 2-aminobenzyl alcohols and alcohols have produced only quinolines via an acceptorless dehydrogenative coupling (corresponding to Scheme 1, steps a and b) utilizing precious[9−11] and recently also base metal[12−16] catalysts, thus falling short of completing the whole BH cycle. Quinolines can be reduced to tetrahydroquinolines via catalytic hydrogenation;[10d,17−19] however, the additional reduction step

Scheme 1. Proposed Borrowing Hydrogen (BH) Cycle for the Synthesis of Tetrahydroquinolines (3)



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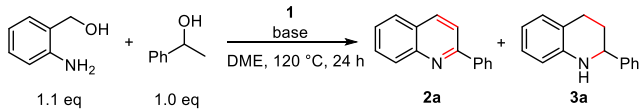
reduces the efficiency of the overall process and reactions with molecular hydrogen often depend on higher pressure (≥15 atm) for catalytic turnover.[17a,d,f−i]

Curiously, efforts to combine the dehydrogenative coupling with catalytic hydrogenation to a full BH cycle are scarce and limited in scope to primary alcohols using a heterogeneous Ni catalyst[20] or the Ru-catalyzed synthesis of tetrahydronaphthyridines.[21] Tetrahydroquinolines have been prepared in an intramolecular N-alkylation reaction via BH,[22] but the necessary amino alcohols have to be prepared in a multistep reaction sequence.

Herein, we disclose the direct synthesis of 1,2,3,4-tetrahydroquinolines starting from 2-aminobenzyl alcohols and secondary alcohols based on the BH strategy utilizing the manganese PN^3 pincer complex **1** (Scheme 1), which exhibited high activity in the N-alkylation of amines with alcohols when activated with KH as base.[23,24]

During our investigations, we observed that the reaction temperature and the applied base influence the outcome of the reaction of 2-aminobenzyl alcohol with 1-phenylethanol drastically. The usage of KO*t*Bu at 140 °C leads to the selective formation of the corresponding 2-phenylquinoline (**2a**) (Table 1, entry 3), with significantly lower catalyst and

Table 1. Optimization of Reaction Conditions for the Synthesis of 2-Phenyl-1,2,3,4-tetrahydroquinoline (3a)[a]



	base			conversion[b] (%)		
no.	type	amt (equiv)	cat. loading (mol %)	**2a**	**3a**	Σ
1	KH[c]	1.00	2.0	57	2	59
2	KO*t*Bu[c]	1.00	2.0	40	10	50
3	KO*t*Bu[c,e]	0.50	2.0	98	<1	98
4	NaH[c]	1.00	2.0	35	8	43
5	KH[c]	1.00	2.0	18	46	64
6	KH[c]	1.25	2.0	18	56	74
7	KH[c]	1.50	2.0	15	59	74
8	KH[c]	1.75	2.0	44	36	80
9	KH[d]	1.50	1.5	5	50	55
10	KH[d]	1.50	2.0	10	65	75
11	KH[d]	1.50	3.0	13	67	80
12	KH + KOH[d]	1.50, 0.30	2.0	12	84	96
13	KH + KOH[d]	1.50, 0.30	2.0[f]	<1	<1	<1

[a]Reaction conditions: 0.275 mmol of 2-aminobenzyl alcohol, 0.250 mmol of 1-phenylethanol, stock solution of **1** in DME (0.005 mmol), closed system, Ar. [b]GC conversion referenced to *p*-xylene. [c]Concentration: 0.3 M, ratio volume reaction mixture/headspace = 1:2. [d]Concentration: 1.0 M, ratio volume reaction mixture/headspace = 1:5. [e]At 140 °C. [f]Cat. = 2 mol % $Mn(CO)_5Br$. Note: Using KH as base led to traces of 1-phenylethanol self-condensation products (<5%).

base loadings in comparison to previous manganese-based catalyst systems.[12] However, catalyst **1** produces preferentially the reduced form (2-phenyl-1,2,3,4-tetrahydroquinoline, **3a**) when a combination of bases, KH and KOH, is employed at 120 °C. As the synthesis of quinolines via dehydrogenative coupling has already been reported with various catalytic systems,[9−16] we decided to focus on the undeveloped formation of 1,2,3,4-tetrahydroquinolines **3**.

A screening was conducted in order to identify the most suitable conditions for the selective formation of the hydrogenated product (Table 1, see also Tables S1−S5). The influence of different solvents (Table S1) revealed that DME combined the highest activity with good selectivity for **3a**.

Among the tested bases (Table 1, entries 1−5), KH led to the highest selectivity for **3a**. The application of 150 mol % of KH is the best choice (Table 1, entry 7), while lower amounts of base decrease the reactivity (Table 1, entries 5 and 6) and higher amounts (Table 1, entry 8) hamper the selectivity of the system for **3a**. The concentration as well as the ratio between reaction volume and headspace have an additional impact on the success of the system (Table 1, entry 7 vs entry 10; Table S3). A substrate concentration of 1.0 M and a 1:5 ratio between volume of reaction mixture and headspace led to the best results. Increasing the catalyst loading to 3.0 mol % only led to a minor improvement in conversion (Table 1, entry 11), whereas a reduction to 1.5 mol % impairs the outcome more clearly (Table 1, entry 9). Attempts to increase the conversion to **3a** further by extending the reaction time had only a minor effect (Table S2).

A challenging problem is the suppression of the self-condensation of 2-aminobenzyl alcohol,[10b] which led to the formation of oligomeric products. In our case, the additional application of KOH (30 mol %) and the order of addition seem to be crucial to minimize this competing side reaction (Table 1, entry 12 and Table S4). No conversion was observed with $Mn(CO)_5Br$ in the absence of the pincer ligand (Table 1, entry 13).

With the optimized reaction conditions in hand, the selectivity of the catalytic system for a broader range of substrates was explored (Table 2). We started our investigations by applying different aromatic secondary alcohols. Generally good yields were obtained.[25−27] The catalytic system tolerates an alcohol containing a ferrocene moiety (**3c**), though a higher catalyst loading (5 mol %) was required when an additional nitrogen atom was present in order to obtain a decent yield (**3d**). A significant decrease in yield was observed when higher substituted alcohols were applied (**3e−3g**). Aliphatic alcohols provided moderate to good conversions in general, providing a facile and atom-efficient access to norangustureine (**3k**), a precursor of the important Hancock alkaloid (±)-angustureine.[28] For products **3i−3k**, the corresponding regioisomers were detected as minor products in diminishing amounts with increasing chain length. A higher catalyst loading was required for the sterically more demanding aliphatic alcohol 3-methylbutan-2-ol to obtain a satisfactory yield of **3l**. Small amounts of 2-(*tert*-butyl)quinoline (**2m**) were observed as the only product for the bulkier 3,3-dimethylbutan-2-ol and no conversion to the corresponding tetrahydroquinoline **3m** was observed. An additional methyl group at the 2-aminobenzyl alcohol was well tolerated, which is reflected by the good yields of **3o−3r**. Even the electron-rich heterocylic (3-aminopyridin-4-yl)methanol readily reacted with 1-phenylethanol, yielding the corresponding 1,2,3,4-tetrahydro-1,7-naphthyridine **3s** in moderate yield. The conversion of 2-aminobenzhydrol to **3t** and **3u** was low, though the dehydrogenative quinoline products were observed as byproducts in relatively large amounts.

In order to prove the feasibility of the catalyst system, the benchmark reaction of 2-aminobenzyl alcohol with 1-phenyl-

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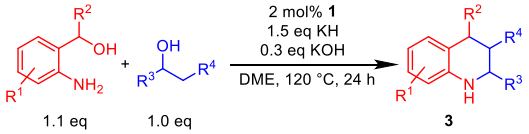
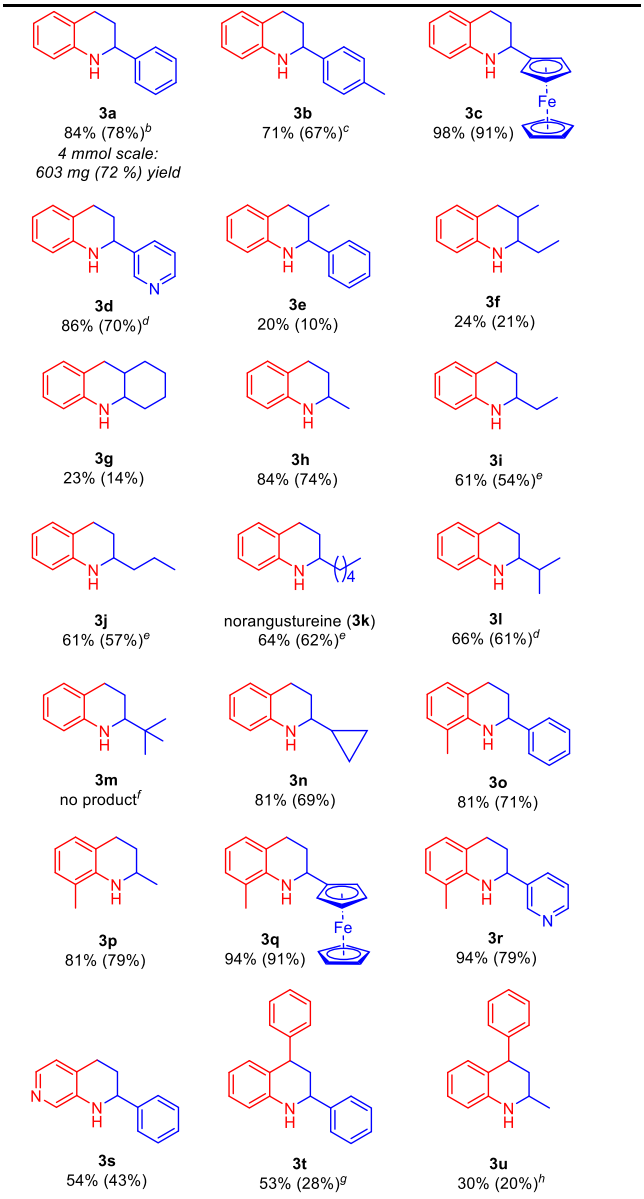
Table 2. Substrate Screening in the Synthesis of 1,2,3,4-Tetrahydroquinolines[a]

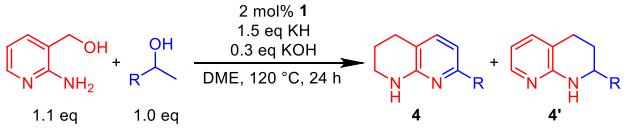


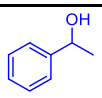
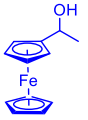
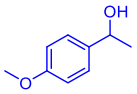


[a]Reaction conditions: 0.880 mmol aminobenzyl alcohol, 0.800 mmol alcohol (1.0 M), stock solution of **1** in DME (0.016 mmol), closed system, Ar, GC conversion referenced to *p*-xylene. Isolated yields are given in parentheses. [b]2% of self-condensation products of 1-phenylethanol. [c]7% of self-condensation products of 4-methyl-1-phenylethanol. [d]5 mol % of **1**. [e]The corresponding regioisomers (**3′**) were detected as minor products: **3i′**: 28% 2,3-dimethyl-1,2,3,4-tetrahydroquinoline (for results of the respective quinoline, see ref 10b); **3j′**: 10% 3-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline; **3k′**: 2% 3-butyl-2-methyl-1,2,3,4-tetrahydroquinoline. [f]12% of 2-(*tert*-butyl)-quinoline (**2m**) was observed. [g]Byproduct: 41% 2,4-diphenylquinoline (**2t**). [h]Byproduct: 67% 2-methyl-4-phenylquinoline (**2u**).

ethanol was performed on a 4 mmol scale to give **3a** in 72% of isolated yield (Table 2).

Table 3. Synthesis of 1,2,3,4-Tetrahydro-1,8-naphthyridines[a]



no.	sec. alcohol	Conversion[b] (Yield)[c] [%] 4		4'	
1		**4a**	89 (73)	**4a'**	<1
2		**4b**	96 (71)	**4b'**	4
3		**4c**	n.d.[d] (24)	**4c'**	n.d.[d] (3)
4		**4d**	59 (51)	**4d'**	27 (15)
5		**4e**	82 (63)	**4e'**	12

[a]Reaction conditions: 0.880 mmol of aminobenzyl alcohol, 0.800 mmol of alcohol (1.0 M), stock solution of **1** in DME (0.016 mmol), closed system, Ar. [b]GC conversion referenced to *p*-xylene. [c]Isolated yield. [d]Full conversion of *p*-methoxy-1-phenylethanol into naphthyridine **4c**, **4c′** and yet unidentified byproducts. n.d. = not detected.

Intrigued by our finding that (3-aminopyridin-4-yl)methanol led to 1,2,3,4-tetrahydro-1,7-naphthyridine **3s**, we explored the reaction with (2-aminopyridin-3-yl)methanol as well (Table 3). Here, the transfer hydrogenation occurs predominantly at the pre-existing pyridyl ring, as noted for the ruthenium-promoted process,[21] leading to 7-substituted 1,2,3,4-tetrahydro-1,8-naphthyridines **4** when the newly formed pyridyl ring bears a conjugated aromatic substituent (Table 3, entries 1−3). The 2-substituted 1,2,3,4-tetrahydro-1,8-naphthyridine **4′** was only observed as a significant byproduct when small aliphatic secondary alcohols were employed (Table 3, entries 4 and 5).

Interestingly, the reaction with *p*-methoxy-1-phenylethanol produced **4c** in 24% yield (Table 3, entry 3) and some yet unidentified byproducts. However, formation of 4-ethylanisole was not observed, in contrast to the respective reaction of *p*-methoxy-1-phenylethanol with 2-aminobenzyl alcohol.[26]

Preliminary mechanistic investigations revealed that 2-ferrocenylquinoline (**2c**) was formed as major product (via GC analysis) within the first 2 h in the reaction of 2-aminobenzyl alcohol with 1-ferrocenylethanol (Table S8, Figure S2).[29] Then the amount of **2c** started to decrease concomitant with formation of the hydrogenated 2-ferrocenyl-1,2,3,4-tetrahydroquinoline (**3c**). No other intermediates of the reaction were detected.

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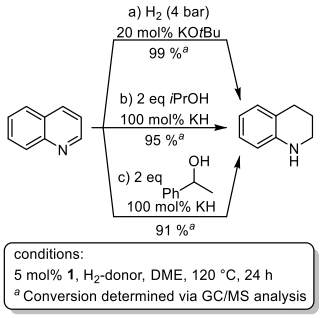
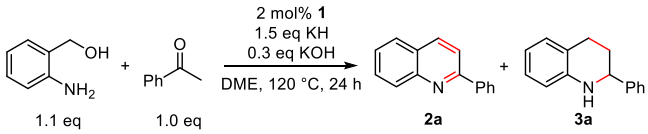
The hydrogenation of quinoline proceeds efficiently using catalyst **1** with external hydrogen (Scheme 2a, Table S9, entries 1−4) requiring significantly lower H_2 pressure (4 bar) compared to known Mn-based catalyst systems (15−80 bar).[17g−i] Furthermore, transfer hydrogenation occurred smoothly with *i*PrOH (Scheme 2b, Table S9, entries 5−8) and 1-phenylethanol (Scheme 2c). Under optimal conditions, 2 equiv of *i*PrOH are employed, whereas larger amounts significantly impaired the result. Transfer hydrogenation of 2-phenylquinoline (**2a**) with *i*PrOH went smoothly (Table S9, entry 12), while 1-phenylethanol was less efficient (Table S9, entry 13), arguably due to the increased steric hindrance and conjugation of the aromatic heterocycle to the 2-phenyl substituent in **2a**.

Scheme 2. Catalytic Hydrogenation of Quinoline with 1 Using Different Hydrogen Sources



Furthermore, the influence of hydrogen atmosphere or hydrogen pressure on the reduction step of the borrowing hydrogen process was investigated using acetophenone as substrate instead of 1-phenylethanol (Table 4). The reaction proceeded under the optimized conditions to form an approximate 1:1 mixture of 2-phenylquinoline (**2a**) and 2-phenyl-1,2,3,4-tetrahydroquinoline (**3a**) (Table 4, entry 1).

Table 4. Influence of Acetophenone on the Distribution of Dehydrogenated and Hydrogenated Product[a]



		conversion[b] (%)		
no.	conditions	**2a**	**3a**	Σ
1	argon (pressurized vial)	49	47	96[c]
2	H_2 (balloon, 1 atm)	75	8	83
3	H_2 (autoclave, 4 bar)	1	76	77

[a]Reaction conditions: 0.250 mmol of acetophenone, 0.275 mmol of 2-aminobenzyl alcohol, concentration 1.0 M, stock solution of **1** in DME (0.005 mmol), Ar. [b]GC/MS conversion. [c]Byproducts: 1,3-diphenylpropan-1-one and chalcone.

This observation can be explained by the presence of an insufficient amount of reducing equivalents, as acetophenone is not a hydrogen donor. Introduction of additional hydrogen with a balloon under atmospheric pressure led to a large excess of quinoline **2a**, while performing the reaction under increased H_2 pressure produced the hydrogenated form **3a** as the major product (Table 4, entry 2 vs entry 3). These observations indicate that catalyst **1** requires a certain pressure of hydrogen for the hydrogenation step, which is attained in our established procedure for the formation of 1,2,3,4-tetrahydroquinolines through heating of the tightly closed vial to 120 °C.

In summary, we have developed a homogeneous catalytic system which facilitates the atom-efficient and selective synthesis of 1,2,3,4-tetrahydroquinolines via a BH process. The combination of the PN^3 manganese pincer complex **1** with the bases KH and KOH allows the formation of a C−C and a C−N single bond in a one-pot reaction. Notably, this cascade reaction can be performed without any additional reducing agent, and the only byproduct generated is water. Various aromatic and aliphatic alcohols lead to good conversions, enabling the straightforward synthesis of valuable nitrogen-containing heterocycles, as exemplified in the synthesis of norangustureine. Besides, the catalytic system shows high activity in the hydrogenation of quinolines by using external hydrogen or via transfer hydrogenation with secondary alcohols as hydrogen donor.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02905.

Experimental procedures, spectral data, ^1H and ^{13}C NMR spectra of all organic products, results of additional catalytic screening reactions, representative GC/FID traces (PDF)

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Notes

The authors declare no competing financial interest.

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