OL | Organic Letters

pubs.acs.org/OrgLett

Letter

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

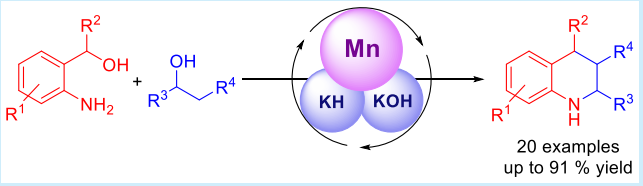
Natalie Hofmann, Leonard Homberg, and Kai C. Hultzsch*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02905

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

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.

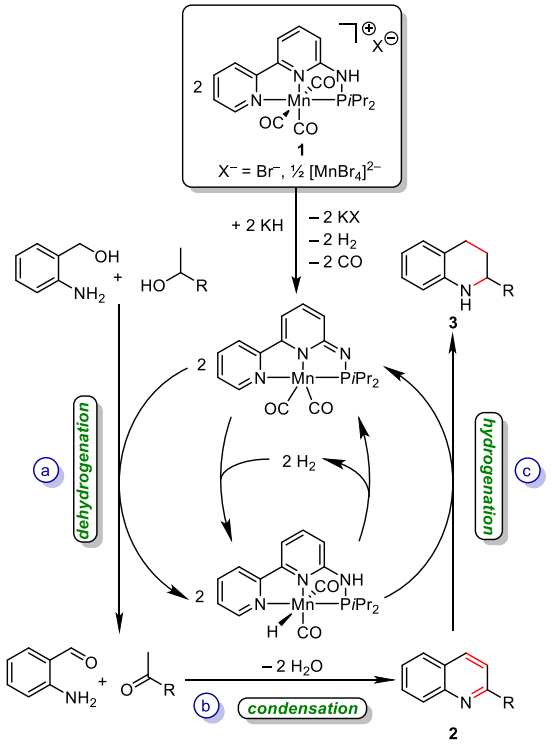


Nitrogen-containing heterocycles are indispensable substructures of important pharmaceuticals and agrochemicals.[1] Within this important substance class, the 1,2,3,4-tetrahydroquinoline[2] scaffold represents a particularly relevant building block for various natural products and pharmacologic active 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)



Received: August 29, 2020

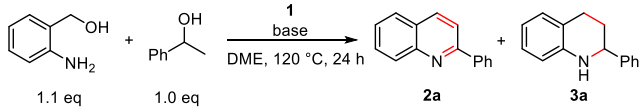
reduces the efficiency of the overall process and reactions with molecular hydrogen often depend on higher pressure (≥15 atm) for catalytic turnover.[17a,d,f−i]

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 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**.

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%).

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).

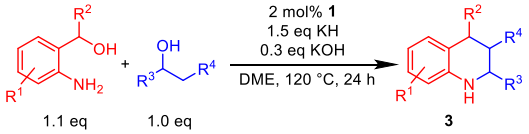
A challenging problem is the suppression of the self-condensation of 2-aminobenzyl alcohol,[10b] which led to the formation of oligomeric products. In our case, the additional application of KOH (30 mol %) and the order of addition seem to be crucial to minimize this competing side reaction (Table 1,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

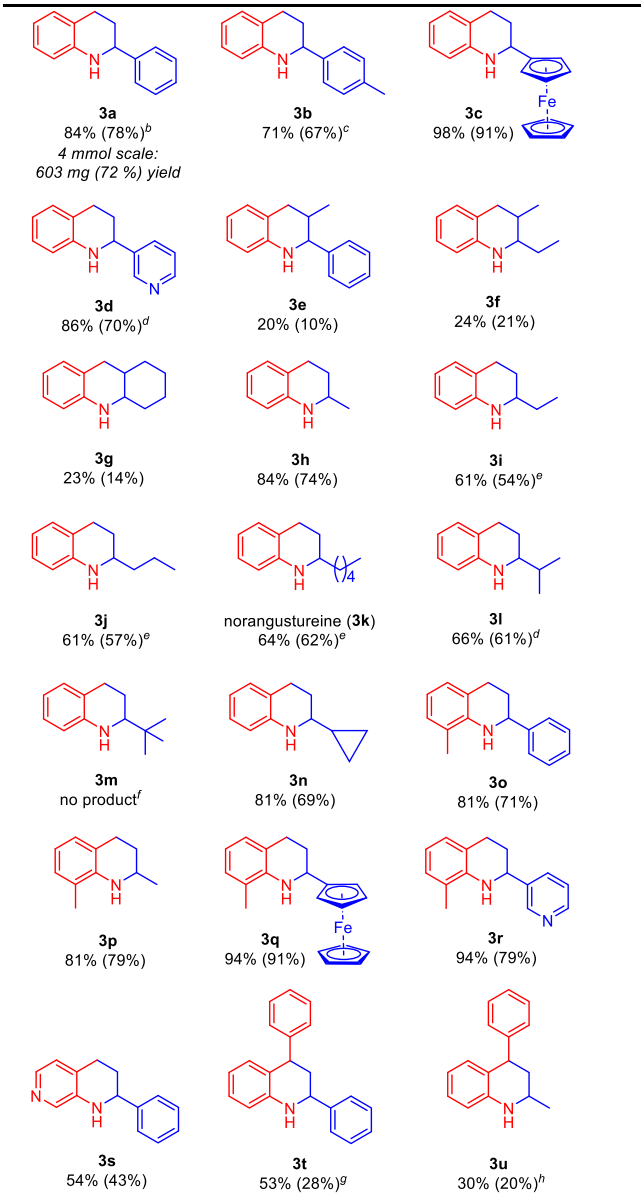
With the optimized reaction conditions in hand, the selectivity of the catalytic system for a broader range of substrates was explored (Table 2). We started our investigations by applying different aromatic secondary alcohols. Generally good yields were obtained.[25−27] The catalytic system tolerates 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-

https://dx.doi.org/10.1021/acs.orglett.0c02905
Org. Lett. XXXX, XXX, XXX−XXX

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

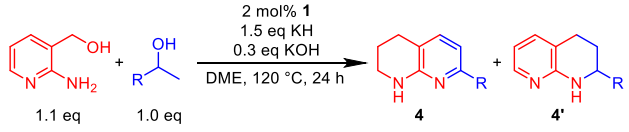


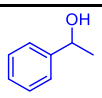
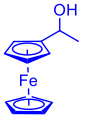
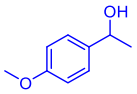


[a]Reaction conditions: 0.880 mmol aminobenzyl alcohol, 0.800 mmol alcohol (1.0 M), stock solution of **1** in DME (0.016 mmol), closed system, Ar, GC conversion referenced to *p*-xylene. Isolated yields are given in parentheses. [b]2% of self-condensation products of 1-phenylethanol. [c]7% of self-condensation 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).

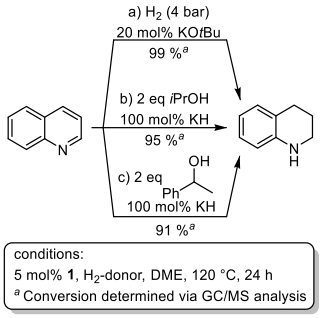
Interestingly, the reaction with *p*-methoxy-1-phenylethanol produced **4c** in 24% yield (Table 3, entry 3) and some yet unidentified byproducts. However, formation of 4-ethylanisole was not observed, in contrast to the respective reaction of *p*-methoxy-1-phenylethanol with 2-aminobenzyl alcohol.[26]

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.

https://dx.doi.org/10.1021/acs.orglett.0c02905
Org. Lett. XXXX, XXX, XXX−XXX

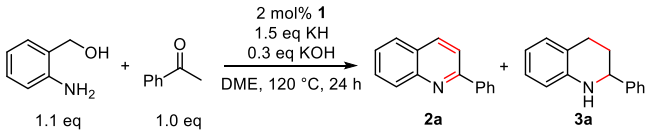
The hydrogenation of quinoline proceeds efficiently using catalyst **1** with external hydrogen (Scheme 2a, Table S9, entries 1−4) requiring significantly lower H_2 pressure (4 bar) compared to known Mn-based catalyst systems (15−80 bar).[17g−i] Furthermore, transfer hydrogenation occurred smoothly with *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)

■ AUTHOR INFORMATION

Corresponding Author

Kai C. Hultzsch − *University of Vienna, Faculty of Chemistry, Institute of Chemical Catalysis, 1090 Vienna, Austria;* orcid.org/0000-0002-5298-035X; Email: kai.hultzsch@univie.ac.at

Authors

Natalie Hofmann − *University of Vienna, Faculty of Chemistry, Institute of Chemical Catalysis, 1090 Vienna, Austria*

Leonard Homberg − *University of Vienna, Faculty of Chemistry, Institute of Chemical Catalysis, 1090 Vienna, Austria*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02905

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) *Amino Group Chemistry: From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2008.

(2) (a) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. Advances in the Chemistry of Tetrahydroquinolines. *Chem. Rev.* **2011**, *111*, 7157−7259. (b) Muthukrishnan, I.; Sridharan, V.; Menéndez, J. C. Progress in the Chemistry of Tetrahydroquinolines. *Chem. Rev.* **2019**, *119*, 5057−5191.

(3) (a) Sheldon, R. A.; Arends, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, 2007. (b) Sheldon, R. A. E. factors, green chemistry and catalysis: an odyssey. *Chem. Commun.* **2008**, 3352−3365.

(4) (a) Watson, A. J.; Williams, J. M. The give and take of alcohol activation. *Science* **2010**, *329*, 635−636. (b) Gunanathan, C.; Milstein, D. Applications of acceptorless dehydrogenation and related trans-

formations in chemical synthesis. *Science* **2013**, *341*, 1229712. (c) Corma, A.; Navas, J.; Sabater, M. J. Advances in One-Pot Synthesis through Borrowing Hydrogen Catalysis. *Chem. Rev.* **2018**, *118*, 1410−1459. (d) Irrgang, T.; Kempe, R. 3d-Metal Catalyzed N- and C-Alkylation Reactions via Borrowing Hydrogen or Hydrogen Autotransfer. *Chem. Rev.* **2019**, *119*, 2524−2549.

(5) (a) Deuss, P. J.; Barta, K.; de Vries, J. G. Homogeneous catalysis for the conversion of biomass and biomass-derived platform chemicals. *Catal. Sci. Technol.* **2014**, *4*, 1174−1196. (b) Li, H.; Guo, H.; Fang, Z.; Aida, T. M.; Smith, R. L. Cycloamination strategies for renewable N-heterocycles. *Green Chem.* **2020**, *22*, 582−611.

(6) Selected reviews on (de)hydrogenations: (a) Dobereiner, G. E.; Crabtree, R. H. Dehydrogenation as a substrate-activating strategy in homogeneous transition-metal catalysis. *Chem. Rev.* **2010**, *110*, 681−702. (b) Gunanathan, C.; Milstein, D. Metal-ligand cooperation by aromatization-dearomatization: a new paradigm in bond activation and "green" catalysis. *Acc. Chem. Res.* **2011**, *44*, 588−602. (c) Obora, Y. Recent Advances in α-Alkylation Reactions using Alcohols with Hydrogen Borrowing Methodologies. *ACS Catal.* **2014**, *4*, 3972−3981. (d) Werkmeister, S.; Neumann, J.; Junge, K.; Beller, M. Pincer-Type Complexes for Catalytic (De)Hydrogenation and Transfer (De)Hydrogenation Reactions: Recent Progress. *Chem. - Eur. J.* **2015**, *21*, 12226−12250. (e) Crabtree, R. H. Homogeneous Transition Metal Catalysis of Acceptorless Dehydrogenative Alcohol Oxidation: Applications in Hydrogen Storage and to Heterocycle Synthesis. *Chem. Rev.* **2017**, *117*, 9228−9246.

(7) Selected reviews on base metal-catalyzed (de)hydrogenation reactions: (a) Zell, T.; Milstein, D. Hydrogenation and Dehydrogenation Iron Pincer Catalysts Capable of Metal-Ligand Cooperation by Aromatization/Dearomatization. *Acc. Chem. Res.* **2015**, *48*, 1979−1994. (b) Garbe, M.; Junge, K.; Beller, M. Homogeneous Catalysis by Manganese-Based Pincer Complexes. *Eur. J. Org. Chem.* **2017**, *2017*, 4344−4362. (c) Maji, B.; Barman, M. Recent Developments of Manganese Complexes for Catalytic Hydrogenation and Dehydrogenation Reactions. *Synthesis* **2017**, *49*, 3377−3393. (d) Kallmeier, F.; Kempe, R. Manganese Complexes for (De)Hydrogenation Catalysis: A Comparison to Cobalt and Iron Catalysts. *Angew. Chem., Int. Ed.* **2018**, *57*, 46−60. (e) Filonenko, G. A.; van Putten, R.; Hensen, E. J. M.; Pidko, E. A. Catalytic (de)hydrogenation promoted by non-precious metals - Co, Fe and Mn: recent advances in an emerging field. *Chem. Soc. Rev.* **2018**, *47*, 1459−1483. (f) Gorgas, N.; Kirchner, K. Isoelectronic Manganese and Iron Hydrogenation/Dehydrogenation Catalysts: Similarities and Divergences. *Acc. Chem. Res.* **2018**, *51*, 1558−1569. (g) Liu, W.; Sahoo, B.; Junge, K.; Beller, M. Cobalt Complexes as an Emerging Class of Catalysts for Homogeneous Hydrogenations. *Acc. Chem. Res.* **2018**, *51*, 1858−1869. (h) Mukherjee, A.; Milstein, D. Homogeneous Catalysis by Cobalt and Manganese Pincer Complexes. *ACS Catal.* **2018**, *8*, 11435−11469. (i) Wei, D.; Darcel, C. Iron Catalysis in Reduction and Hydrometalation Reactions. *Chem. Rev.* **2019**, *119*, 2550−2610. (j) Junge, K.; Papa, V.; Beller, M. Cobalt-Pincer Complexes in Catalysis. *Chem. - Eur. J.* **2019**, *25*, 122−143. (k) Waiba, S.; Maji, B. Manganese Catalyzed Acceptorless Dehydrogenative Coupling Reactions. *ChemCatChem* **2020**, *12*, 1891−1902.

(8) Selected examples for applications of Mn in BH and acceptorless dehydrogenative coupling reactions: (a) Mukherjee, A.; Nerush, A.; Leitus, G.; Shimon, L. J.; Ben-David, Y.; Espinosa Jalapa, N. A.; Milstein, D. Manganese-Catalyzed Environmentally Benign Dehydrogenative Coupling of Alcohols and Amines to Form Aldimines and H_2: A Catalytic and Mechanistic Study. *J. Am. Chem. Soc.* **2016**, *138*, 4298−4301. (b) Elangovan, S.; Neumann, J.; Sortais, J. B.; Junge, K.; Darcel, C.; Beller, M. Efficient and selective N-alkylation of amines with alcohols catalysed by manganese pincer complexes. *Nat. Commun.* **2016**, *7*, 12641. (c) Pena-Lopez, M.; Piehl, P.; Elangovan, S.; Neumann, H.; Beller, M. Manganese-Catalyzed Hydrogen-Autotransfer C-C Bond Formation: α-Alkylation of Ketones with Primary Alcohols. *Angew. Chem., Int. Ed.* **2016**, *55*, 14967−14971. (d) Mastalir, M.; Pittenauer, E.; Allmaier, G.; Kirchner, K. Manganese-Catalyzed Aminomethylation of Aromatic Compounds with Methanol as a Sustainable C1 Building Block. *J. Am. Chem. Soc.* **2017**, *139*, 8812−8815. (e) Fu, S.; Shao, Z.; Wang, Y.; Liu, Q. Manganese-Catalyzed Upgrading of Ethanol into 1-Butanol. *J. Am. Chem. Soc.* **2017**, *139*, 11941−11948. (f) Deibl, N.; Kempe, R. Manganese-Catalyzed Multicomponent Synthesis of Pyrimidines from Alcohols and Amidines. *Angew. Chem., Int. Ed.* **2017**, *56*, 1663−1666. (g) Kallmeier, F.; Dudziec, B.; Irrgang, T.; Kempe, R. Manganese-Catalyzed Sustainable Synthesis of Pyrroles from Alcohols and Amino Alcohols. *Angew. Chem., Int. Ed.* **2017**, *56*, 7261−7265. (h) Zhang, G.; Irrgang, T.; Dietel, T.; Kallmeier, F.; Kempe, R. Manganese-Catalyzed Dehydrogenative Alkylation or α-Olefination of Alkyl-Substituted N-Heteroarenes with Alcohols. *Angew. Chem., Int. Ed.* **2018**, *57*, 9131−9135. (i) Wang, Y.; Shao, Z.; Zhang, K.; Liu, Q. Manganese-Catalyzed Dual-Deoxygenative Coupling of Primary Alcohols with 2-Arylethanols. *Angew. Chem., Int. Ed.* **2018**, *57*, 15143−15147. (j) Barman, M. K.; Jana, A.; Maji, B. Phosphine-Free NNN-Manganese Complex Catalyzed α-Alkylation of Ketones with Primary Alcohols and Friedländer Quinoline Synthesis. *Adv. Synth. Catal.* **2018**, *360*, 3233−3238. (k) Daw, P.; Kumar, A.; Espinosa-Jalapa, N. A.; Diskin-Posner, Y.; Ben-David, Y.; Milstein, D. Synthesis of Pyrazines and Quinoxalines via Acceptorless Dehydrogenative Coupling Routes Catalyzed by Manganese Pincer Complexes. *ACS Catal.* **2018**, *8*, 7734−7741. (l) Masdemont, J.; Luque-Urrutia, J. A.; Gimferrer, M.; Milstein, D.; Poater, A. Mechanism of Coupling of Alcohols and Amines To Generate Aldimines and H_2 by a Pincer Manganese Catalyst. *ACS Catal.* **2019**, *9*, 1662−1669. (m) Freitag, F.; Irrgang, T.; Kempe, R. Mechanistic Studies of Hydride Transfer to Imines from a Highly Active and Chemoselective Manganate Catalyst. *J. Am. Chem. Soc.* **2019**, *141*, 11677−11685. (n) Bruneau-Voisine, A.; Pallova, L.; Bastin, S.; César, V.; Sortais, J.-B. Manganese catalyzed α-methylation of ketones with methanol as a C1 source. *Chem. Commun.* **2019**, *55*, 314−317. (o) Borghs, J. C.; Lebedev, Y.; Rueping, M.; El-Sepelgy, O. Sustainable Manganese-Catalyzed Solvent-Free Synthesis of Pyrroles from 1,4-Diols and Primary Amines. *Org. Lett.* **2019**, *21*, 70−74. (p) Das, K.; Mondal, A.; Pal, D.; Srimani, D. Sustainable Synthesis of Quinazoline and 2-Aminoquinoline via Dehydrogenative Coupling of 2-Aminobenzyl Alcohol and Nitrile Catalyzed by Phosphine-Free Manganese Pincer Complex. *Org. Lett.* **2019**, *21*, 3223−3227. (q) Kaithal, A.; Gracia, L. L.; Camp, C.; Quadrelli, E. A.; Leitner, W. Direct Synthesis of Cycloalkanes from Diols and Secondary Alcohols or Ketones Using a Homogeneous Manganese Catalyst. *J. Am. Chem. Soc.* **2019**, *141*, 17487−17492. (r) Shao, Z.; Li, Y.; Liu, C.; Ai, W.; Luo, S.-P.; Liu, Q. Reversible interconversion between methanol-diamine and diamide for hydrogen storage based on manganese catalyzed (de)hydrogenation. *Nat. Commun.* **2020**, *11*, 591. (s) Kaithal, A.; van Bonn, P.; Hölscher, M.; Leitner, W. Manganese(I)-Catalyzed β-Methylation of Alcohols Using Methanol as C_1 Source. *Angew. Chem., Int. Ed.* **2020**, *59*, 215−220. (t) Jana, A.; Das, K.; Kundu, A.; Thorve, P. R.; Adhikari, D.; Maji, B. A Phosphine-Free Manganese Catalyst Enables Stereoselective Synthesis of (1 + *n*)-Membered Cycloalkanes from Methyl Ketones and 1,*n*-Diols. *ACS Catal.* **2020**, *10*, 2615−2626.

(9) Re: (a) Mastalir, M.; Glatz, M.; Pittenauer, E.; Allmaier, G.; Kirchner, K. Rhenium-Catalyzed Dehydrogenative Coupling of Alcohols and Amines to Afford Nitrogen-Containing Aromatics and More. *Org. Lett.* **2019**, *21*, 1116−1120. (b) Wei, D.; Dorcet, V.; Darcel, C.; Sortais, J.-B. Synthesis of Quinolines Through Acceptorless Dehydrogenative Coupling Catalyzed by Rhenium PN(H)P Complexes. *ChemSusChem* **2019**, *12*, 3078−3082.

(10) Selected examples for Ru: (a) Chai, H.; Wang, L.; Liu, T.; Yu, Z. A Versatile Ru(II)-NNP Complex Catalyst for the Synthesis of Multisubstituted Pyrroles and Pyridines. *Organometallics* **2017**, *36*, 4936−4942. (b) Guo, B.; Yu, T.-Q.; Li, H.-X.; Zhang, S.-Q.; Braunstein, P.; Young, D. J.; Li, H.-Y.; Lang, J.-P. Phosphine Ligand-Free Ruthenium Complexes as Efficient Catalysts for the Synthesis of Quinolines and Pyridines by Acceptorless Dehydrogenative Coupling Reactions. *ChemCatChem* **2019**, *11*, 2500−2510. (c) Donthireddy, S. N. R.; Mathoor Illam, P.; Rit, A. Ruthenium(II) Complexes of Heteroditopic N-Heterocyclic Carbene Ligands: Efficient Catalysts

https://dx.doi.org/10.1021/acs.orglett.0c02905
Org. Lett. XXXX, XXX, XXX−XXX

for C−N Bond Formation via a Hydrogen-Borrowing Strategy under Solvent-Free Conditions. *Inorg. Chem.* **2020**, *59*, 1835−1847. (d) Yun, X.-J.; Zhu, J.-W.; Jin, Y.; Deng, W.; Yao, Z.-J. Half-Sandwich Ruthenium Complexes for One-Pot Synthesis of Quinolines and Tetrahydroquinolines: Diverse Catalytic Activity in the Coupled Cyclization and Hydrogenation Process. *Inorg. Chem.* **2020**, *59*, 7841−7851.

(11) Ir: Ruch, S.; Irrgang, T.; Kempe, R. New Iridium Catalysts for the Selective Alkylation of Amines by Alcohols under Mild Conditions and for the Synthesis of Quinolines by Acceptor-less Dehydrogenative Condensation. *Chem. - Eur. J.* **2014**, *20*, 13279−13285.

(12) Mn: (a) Mastalir, M.; Glatz, M.; Pittenauer, E.; Allmaier, G.; Kirchner, K. Sustainable Synthesis of Quinolines and Pyrimidines Catalyzed by Manganese PNP Pincer Complexes. *J. Am. Chem. Soc.* **2016**, *138*, 15543−15546. (b) Das, K.; Mondal, A.; Srimani, D. Phosphine free Mn-complex catalysed dehydrogenative C-C and C-heteroatom bond formation: a sustainable approach to synthesize quinoxaline, pyrazine, benzothiazole and quinoline derivatives. *Chem. Commun.* **2018**, *54*, 10582−10585. (c) Azizi, K.; Akrami, S.; Madsen, R. Manganese(III) Porphyrin-Catalyzed Dehydrogenation of Alcohols to form Imines, Tertiary Amines and Quinolines. *Chem. - Eur. J.* **2019**, *25*, 6439−6446.

(13) Fe: Elangovan, S.; Sortais, J.-B.; Beller, M.; Darcel, C. Iron-Catalyzed α-Alkylation of Ketones with Alcohols. *Angew. Chem., Int. Ed.* **2015**, *54*, 14483−14486.

(14) Co: (a) Zhang, G.; Wu, J.; Zeng, H.; Zhang, S.; Yin, Z.; Zheng, S. Cobalt-Catalyzed α-Alkylation of Ketones with Primary Alcohols. *Org. Lett.* **2017**, *19*, 1080−1083. (b) Midya, S. P.; Landge, V. G.; Sahoo, M. K.; Rana, J.; Balaraman, E. Cobalt-catalyzed acceptorless dehydrogenative coupling of aminoalcohols with alcohols: direct access to pyrrole, pyridine and pyrazine derivatives. *Chem. Commun.* **2018**, *54*, 90−93. (c) Shee, S.; Ganguli, K.; Jana, K.; Kundu, S. Cobalt complex catalyzed atom-economical synthesis of quinoxaline, quinoline and 2-alkylaminoquinoline derivatives. *Chem. Commun.* **2018**, *54*, 6883−6886.

(15) Ni: (a) Das, S.; Maiti, D.; De Sarkar, S. Synthesis of Polysubstituted Quinolines from α-2-Aminoaryl Alcohols Via Nickel-Catalyzed Dehydrogenative Coupling. *J. Org. Chem.* **2018**, *83*, 2309−2316. (b) Parua, S.; Sikari, R.; Sinha, S.; Das, S.; Chakraborty, G.; Paul, N. D. A nickel catalyzed acceptorless dehydrogenative approach to quinolines. *Org. Biomol. Chem.* **2018**, *16*, 274−284.

(16) Cu: Tan, D.-W.; Li, H.-X.; Zhu, D.-L.; Li, H.-Y.; Young, D. J.; Yao, J.-L.; Lang, J.-P. Ligand-Controlled Copper(I)-Catalyzed Cross-Coupling of Secondary and Primary Alcohols to α-Alkylated Ketones, Pyridines, and Quinolines. *Org. Lett.* **2018**, *20*, 608−611.

(17) Selected examples using molecular hydrogen: (a) Wang, D. S.; Chen, Q. A.; Lu, S. M.; Zhou, Y. G. Asymmetric Hydrogenation of Heteroarenes and Arenes. *Chem. Rev.* **2012**, *112*, 2557−2590. See also references cited therein. (b) Chakraborty, S.; Brennessel, W. W.; Jones, W. D. A Molecular Iron Catalyst for the Acceptorless Dehydrogenation and Hydrogenation of N-Heterocycles. *J. Am. Chem. Soc.* **2014**, *136*, 8564−8567. (c) Xu, R.; Chakraborty, S.; Yuan, H.; Jones, W. D. Acceptorless, Reversible Dehydrogenation and Hydrogenation of N-Heterocycles with a Cobalt Pincer Catalyst. *ACS Catal.* **2015**, *5*, 6350−6354. (d) Luo, Y. E.; He, Y. M.; Fan, Q. H. Asymmetric Hydrogenation of Quinoline Derivatives Catalyzed by Cationic Transition Metal Complexes of Chiral Diamine Ligands: Scope, Mechanism and Catalyst Recycling. *Chem. Rec.* **2016**, *16*, 2697−2711. (e) Adam, R.; Cabrero-Antonino, J. R.; Spannenberg, A.; Junge, K.; Jackstell, R.; Beller, M. A General and Highly Selective Cobalt-Catalyzed Hydrogenation of N-Heteroarenes under Mild Reaction Conditions. *Angew. Chem., Int. Ed.* **2017**, *56*, 3216−3220. (f) Sahoo, B.; Kreyenschulte, C.; Agostini, G.; Lund, H.; Bachmann, S.; Scalone, M.; Junge, K.; Beller, M. A robust iron catalyst for the selective hydrogenation of substituted (iso)quinolones. *Chem. Sci.* **2018**, *9*, 8134−8141. (g) Wang, Y.; Zhu, L.; Shao, Z.; Li, G.; Lan, Y.; Liu, Q. Unmasking the Ligand Effect in Manganese-Catalyzed Hydrogenation: Mechanistic Insight and Catalytic Application. *J. Am. Chem. Soc.* **2019**, *141*, 17337−17349. (h) Papa, V.; Cao, Y.; Spannenberg, A.; Junge, K.; Beller, M. Development of a practical non-noble metal catalyst for hydrogenation of N-heteroarenes. *Nat. Catal.* **2020**, *3*, 135. (i) Wang, Z.; Chen, L.; Mao, G.; Wang, C. Simple manganese carbonyl catalyzed hydrogenation of quinolines and imines. *Chin. Chem. Lett.* **2020**, *31*, 1890−1894.

(18) Selected examples using transfer hydrogenation: (a) Cabrero-Antonino, J. R.; Adam, R.; Junge, K.; Jackstell, R.; Beller, M. Cobalt-catalysed transfer hydrogenation of quinolines and related heterocycles using formic acid under mild conditions. *Catal. Sci. Technol.* **2017**, *7*, 1981−1985. (b) Dubey, A.; Rahaman, S. M. W.; Fayzullin, R. R.; Khusnutdinova, J. R. Transfer Hydrogenation of Carbonyl Groups, Imines and N-Heterocycles Catalyzed by Simple, Bipyridine-Based Mn^{I} Complexes. *ChemCatChem* **2019**, *11*, 3844−3852.

(19) For the Mn-catalyzed (de)hydrogenation of other N-heterocycles, see: Zubar, V.; Borghs, J. C.; Rueping, M. Hydrogenation or Dehydrogenation of N-Containing Heterocycles Catalyzed by a Single Manganese Complex. *Org. Lett.* **2020**, *22*, 3974−3978.

(20) Zhang, J.; An, Z.; Zhu, Y.; Shu, X.; Song, H.; Jiang, Y.; Wang, W.; Xiang, X.; Xu, L.; He, J. $Ni^{0}/Ni^{\delta+}$ Synergistic Catalysis on a Nanosized Ni Surface for Simultaneous Formation of C−C and C−N Bonds. *ACS Catal.* **2019**, *9*, 11438−11446.

(21) Xiong, B.; Li, Y.; Lv, W.; Tan, Z.; Jiang, H.; Zhang, M. Ruthenium-Catalyzed Straightforward Synthesis of 1,2,3,4-Tetrahydronaphthyridines via Selective Transfer Hydrogenation of Pyridyl Ring with Alcohols. *Org. Lett.* **2015**, *17*, 4054−4057.

(22) (a) Fujita, K.; Yamamoto, K.; Yamaguchi, R. Oxidative cyclization of amino alcohols catalyzed by a CpIr complex. Synthesis of indoles, 1,2,3,4-tetrahydroquinolines, and 2,3,4,5-tetrahydro-1-benzazepine. *Org. Lett.* **2002**, *4*, 2691−2694. (b) Lim, C. S.; Quach, T. T.; Zhao, Y. Enantioselective Synthesis of Tetrahydroquinolines by Borrowing Hydrogen Methodology: Cooperative Catalysis by an Achiral Iridacycle and a Chiral Phosphoric Acid. *Angew. Chem., Int. Ed.* **2017**, *56*, 7176−7180.

(23) Homberg, L.; Roller, A.; Hultzsch, K. C. A Highly Active PN^{3} Manganese Pincer Complex Performing N-Alkylation of Amines under Mild Conditions. *Org. Lett.* **2019**, *21*, 3142−3147.

(24) In complex **1**, the metal and the ligand are thought to be involved in the bond activation of the (de)hydrogenation process. For a review on this concept of metal−ligand cooperation, see: Khusnutdinova, J. R.; Milstein, D. Metal-Ligand Cooperation. *Angew. Chem., Int. Ed.* **2015**, *54*, 12236−12273.

(25) Attempts to use *p*-bromo-1-phenylethanol led to loss of bromine during the reaction, and the dehydrogenated 2-phenylquinoline (**2a**) was detected as the major product (53%). Similar results were also obtained at lower reaction temperatures (80 °C). Further investigations revealed that bromobenzene was hydrodehalogenated under the general reaction conditions, whereas no reaction was observed under these conditions in the absence of the Mn pincer complex. Besides, hydrodehalogenation was also observed for (2-amino-5-chlorophenyl)methanol as starting material, indicating that aryl chlorides and bromides are not tolerated under these reactions conditions in general. This stands in marked contrast to our finding that aromatic halide substituents are generally tolerated under conditions applied in the N-alkylation of alcohols; see ref 23. However, hydrodehalogenation can be facilitated by a number of catalyst systems, and it is a known competition reaction during the catalytic hydrogenation of halogenated compounds; see: (a) Sisak, A.; Simon, O. B. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; Vol. 3, pp 513−546. (b) Formenti, D.; Ferretti, F.; Scharnagl, F. K.; Beller, M. Reduction of Nitro Compounds Using 3d-Non-Noble Metal Catalysts. *Chem. Rev.* **2019**, *119*, 2611−2680.

(26) The reaction with *p*-methoxy-1-phenylethanol produced 4-ethylanisole (83% conv by GC/MS analysis) rather than the corresponding quinoline or 1,2,3,4-tetrahydroquinoline, suggesting that the alcohol is acting as a PMB-protecting group that is cleaved under the prevalent reaction conditions.

https://dx.doi.org/10.1021/acs.orglett.0c02905
Org. Lett. XXXX, XXX, XXX−XXX

(27) 1-(2-Furanyl)ethanol and 1-(2-thienyl)ethanol were tested as substrates as well. However, these reactions only led to traces of the corresponding tetrahydroquinolines (<5% based on GC/MS analysis) and yet unidentified byproducts.
(28) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. The Hancock Alkaloids Angustureine, Cuspareine, Galipinine, and Galipeine: A Review of their Isolation, Synthesis, and Spectroscopic Data. *Eur. J. Org. Chem.* **2019**, *2019*, 5093−5119.
(29) Similar observations were made for the reaction of 2-aminobenzyl alcohol with *i*PrOH in which the reaction rate decreased significantly after 4 h (Table S7, Figure S1).

https://dx.doi.org/10.1021/acs.orglett.0c02905
Org. Lett. XXXX, XXX, XXX−XXX