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Benzylamines *via* iron catalyzed direct amination of benzyl alcohols

Tao Yan, Ben L. Feringa, Katalin Barta*

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ABSTRACT: Benzylamines play a prominent role in numerous pharmaceutically active compounds. Thus, the development of novel, sustainable catalytic methodologies to provide access to these privileged structural motifs is of central importance. Herein we describe a systematic study for the construction of a large variety of benzylamines using a well-defined homogeneous iron-complex. The methodology consists of the direct coupling of readily available benzyl alcohols with simpler amines through the borrowing hydrogen methodology producing a variety of substituted secondary and tertiary benzylamines in moderate to excellent yields for the first time with an iron catalyst. Notably, we explore the versatility of this methodology in the one-pot synthesis of non-symmetric tertiary amines, sequential functionalization of diols with distinctly different amines as well as the synthesis of *N*-benzyl piperidines via various synthetic pathways. In addition, direct conversion of renewable building block 2,5-furan-dimethanol to pharmaceutically relevant compounds is achieved.

KEYWORDS: *iron catalysis, borrowing hydrogen, homogenous catalysis, benzylamines, alcohol to amine transformation*

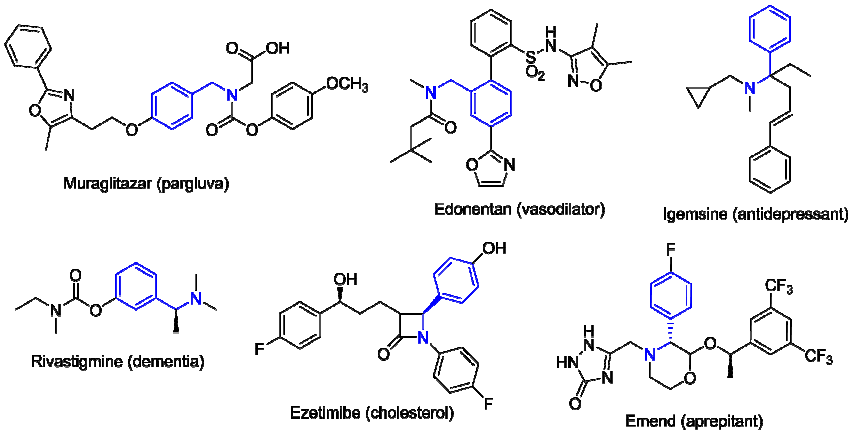
INTRODUCTION

Benzylamines are frequently encountered motifs in biological systems, and are highly valuable targets due to their versatility[1] (**Scheme 1**). Many pharmaceuticals contain a benzylamine moiety. Prominent examples include Rivastigmine[1b], a cholinergic agent for treating dementia due to Parkinson's disease; Ezetimibe[1c], a drug that helps reducing plasma cholesterol levels; and Emend[1d], an aprepitant that blocks the neurokinin 1 (NK_1) receptor. Developing efficient pathways that allow for selective synthesis of benzylamines, especially starting from readily available substrates using sustainable catalysts based on non-toxic and inexpensive metals is an important goal[2,3,4].

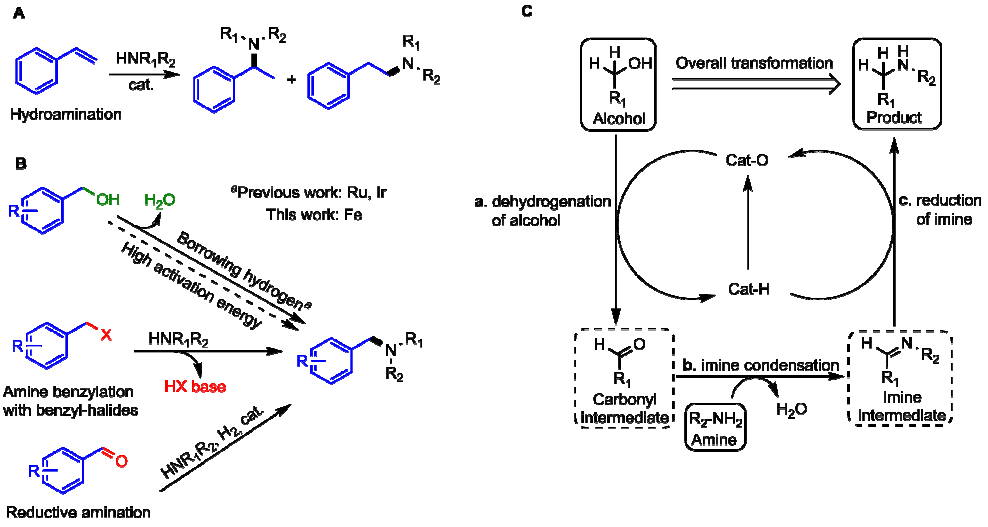
Methods for the synthesis of benzylamine derivatives are shown in **Scheme 2**, **A** and **B**. Catalytic hydroamination of alkenes or alkynes is an efficient way to access 1-methyl-benzylamines.[2] Alternatively, benzylation of amines with benzyl halides *via* nucleophilic substitution[3] leads to the formation of stoichiometric amounts of waste. Reductive amination[4] is a catalytic and atom-economic alternative, however here the aldehyde reaction partner is usually generated by selective alcohol oxidation representing an additional reaction step, moreover, aldol-condensation is a frequent side reaction.

Among these methods, direct amination of benzyl alcohols is a preferred method because these substrates are readily available and can even be obtained from renewable resources[5,6], making this route a highly sustainable alternative. However, direct nucleophilic substitution of the hydroxyl group of benzyl alcohols with amines is an energy and cost intensive process[7,8], while, installing a good leaving group instead of the hydroxyl functionality will suffer from low atom-efficiency. The desired, catalytic way to perform the direct coupling of benzyl alcohols with amines involves the borrowing hydrogen[9] strategy (**Scheme 2**, **C**). In this case, a specific sequence of reaction steps will occur: dehydrogenation of alcohol to aldehyde (**a**), imine formation (**b**) reduction of imine (**c**), which maintain the high atom-efficiency[10] while requiring much lower activation energy[9c]. Addi-

Scheme 1. Bio-active compounds which are based on benzylamines as building blocks.



Scheme 2. Comparison of synthetic pathways to access benzylamine derivatives. **A** Hydroamination of styrene with amine. **B** Comparison of amination of benzyl alcohols, benzyl halides and benzyl aldehydes. **C** Catalytic amination of alcohols through borrowing hydrogen.



tionally, this method provides innocuous water as the only side product.

Since the first examples of catalytic amination of alcohols through borrowing hydrogen reported by Grigg[11] and Watanabe[12] in 1981, considerable progress has been made in this area[13]. However, mostly precious metal catalysts containing ruthenium[14] or iridium[15] were used. Biorelevant and abundant transition metals like iron, have been only scarcely used for this transformation[16,18,19].

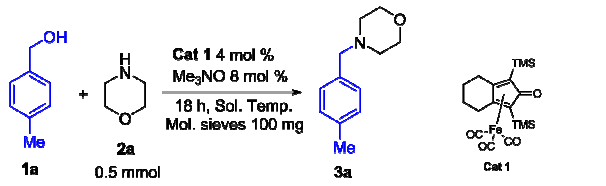
Recently, we reported the first example of a sustainable, direct amination of alcohols catalyzed by a well-defined iron[17] complex through the borrowing hydrogen strategy.[18] This work focused on the use of diverse aromatic amines and aliphatic alcohols and diols. Two examples were also included using benzyl alcohol as substrate, however, these reactions suffered from rather low yields. Very recently, Wills and coworkers also reported on the iron catalyzed amination of alcohols[19a]. Examples of benzyl alcohol amination, primarily with aniline were described, however no product formation was observed when benzylamine was employed as the reaction partner to benzyl alcohols. Later, Zhao and coworkers reported iron catalyzed amination of secondary alcohols with assistant of 0.4 equiv AgF[19b]. However, only very limited success has been shown with use of benzyl alcohols.

Here, a highly versatile method for the synthesis of a large variety of benzylamines through direct iron catalyzed amination of benzyl alcohols is presented. In addition to the impressive scope, important novel aspects are the one-pot synthesis of asymmetric tertiary amines as well as uncovering the reactivity trends in the sequential functionalization of benzyl alcohols. Moreover, fully sustainable, two step pathways from cellulosic platform chemicals to pharmaceutically active compounds is described.

RESULTS AND DISCUSSION

Optimization of reaction conditions. 4-Methylbenzyl alcohol (**1a**) and morpholine (**2a**) were selected as the starting materials for optimization of the reaction conditions for direct coupling of benzyl-alcohols with secondary amines (**Table 1**). Using our previously reported conditions[18] with additional assistance of molecular sieves,

Table 1. Optimization of reaction conditions for amination of 4-methylbenzyl alcohol (**1a**) with morpholine (**2a**).[a]



Entry	**1a** [mmol]	Solvent	T [°C]	Conversion [%][b]
1	1 (2 equiv.)	CPME	130	39
2	1	THF	130	33
3	1	Dioxane	130	30
4	1	DCE	130	>95[c]
5	1	CH_3CN	130	<5
6	1	DMF	130	<5
7	1	Toluene	130	64
8[d]	1	Toluene	130	<5
9[e]	1	Toluene	130	<5
10[f]	1	Toluene	130	<5
11	1	Toluene	135	87
12	1	CPME	135	82
13	2 (4 equiv.)	Toluene	135	>95 (87)

[a]**General reaction conditions**: **General Procedure** (see Supporting information, page S2), 0.5 mmol **2a**, 2 or 4 equiv. **1a**, 0.04 equiv. **Cat 1**, 0.08 equiv. Me_3NO, 2 ml solvent, 18 h, 130 or 135 °C, 95 - 105 mg molecular sieves, unless otherwise specified, isolated yield in parenthesis. [b]Conversion was determined by GC-FID using decane as the internal standard. [c]No **3a** has been observed based on GC-MS. [d]4 mol% $FeCl_3$ instead of **Cat 1** and Me_3NO. [e]2 mol% $Fe_2(CO)_9$ instead of **Cat 1** and Me_3NO. [f]4 mol% Iron(II) phthalocyanine instead of **Cat 1** and Me_3NO.

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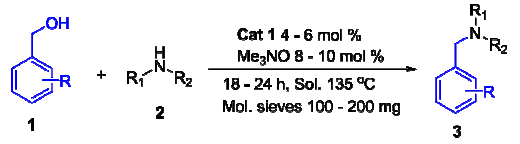
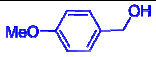
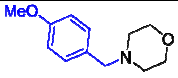
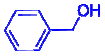
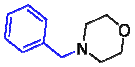
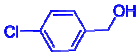
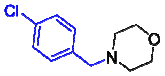
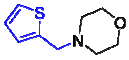
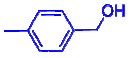
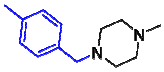
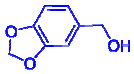
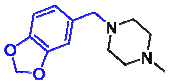
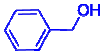
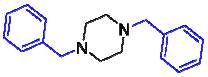
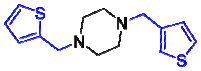
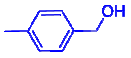
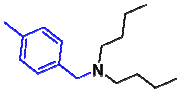
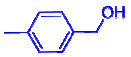
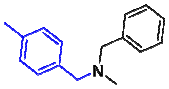
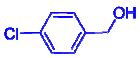
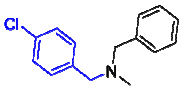
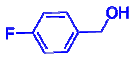
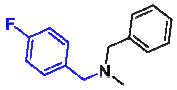
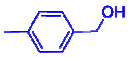
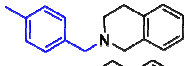
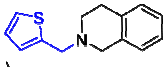
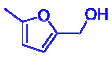
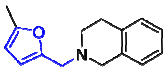
only 39 % conversion was obtained (**Table 1**, entry 1). A solvent screening showed, that etherate solvents like tetrahydrofuran (THF) and dioxane gave low conversions (33 % and 30 %, respectively, **Table 1**, entries 2 and 3). Dichloroethane (DCE) gave full conversion but the desired product (**3a**) was not detected presumably due to nucleophilic substitution of the solvent (DCE) with morpholine (**2a**) (**Table 1**, entry 4). More polar solvents like acetonitrile and dimethylformamide (DMF) gave very poor conversion (**Table 1**, entries 5 and 6). In toluene, 64 % conversion was obtained (**Table 1**, entry 7). When other iron sources like $FeCl_3$, $Fe_2(CO)_9$ or Iron(II) phtalocyanine were applied instead of **Cat 1**, the conversions were unsatisfactory (**Table 1**, entries 8 - 10). Using **Cat1**, the conversion improved to 87 % when increasing the temperature to 135 °C in toluene, probably due to the acceleration of imine reduction (**Table 1**, entry 11). Similar results were obtained in CPME at 135 °C (82 %, **Table 1**, entry 12).

Table 2. Amination of benzyl alcohols with secondary amines.[a]



Entry	Substrate **1**	Product **3**	Yield [%][b]
1	**1b** 	**3b** 	88
2	**1c** 	**3c** 	60
3	**1d** 	**3d** 	40
4	**1e** 	**3e** 	74
5	**1a** 	**3f** 	78
6	**1f** 	**3g** 	69
7	**1c** 	**3h** 	90
8	**1e** 	**3i** 	80
9	**1a** 	**3j** 	65
10	**1a** 	**3k** 	91
11	**1d** 	**3l** 	63
12	**1g** 	**3m** 	69
13	**1a** 	**3n** 	89
14	**1e** 	**3o** 	79
15	**1h** 	**3p** 	59

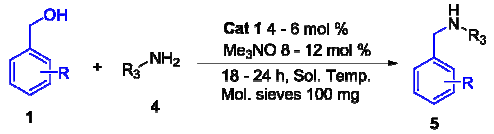
[a]**General reaction conditions**: **General Procedure** (see Supporting information, page S2), 0.5 mmol **2**, 2 mmol **1a**, 0.02 – 0.03 mmol **Cat 1**, 0.04 - 0.06 mmol Me_3NO, 2 ml solvent, 18 - 24 h, 135 °C, 95 - 105 mg molecular sieves,for specified conditions see Supporting information, **Table S2a** and **Table S2b**. [b]Isolated yields.

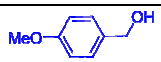
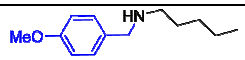
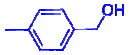
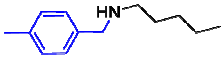
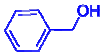
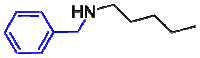
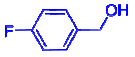
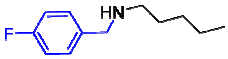
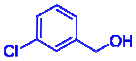
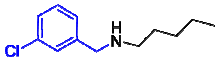
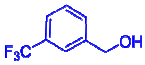
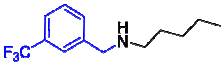
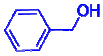
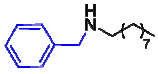
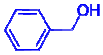
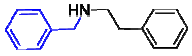
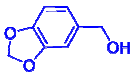
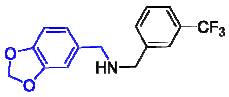
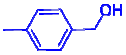
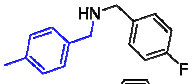
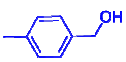
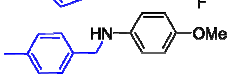
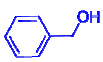
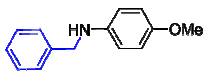
Increasing the loading of **1a** to 2 mmol in toluene gave full conversion and 87 % isolated yield of **3a** (**Table 1**, entry 13).

Reactions of benzyl alcohols with secondary amines. Next, under optimized reaction conditions, a variety of secondary amines and benzyl alcohols were tested (**Table 2**). Benzyl alcohol **1b** with an electron-donating $-OCH_3$ substituent reacted smoothly with **2a** providing full conversion and 88 % isolated yield of **3b** (**Table 2**, entry 1). When less electron rich substrates **1c** and **1d** were employed, lower reactivity was observed; 60 % of **3c** and 40 % of **3d** were isolated after 18 and 24 h reaction time, respectively (**Table 2**, entries 2 and 3). Interestingly, also for 2-thiophenemethanol (**1e**), a high isolated yield (74 %) of **3e** was obtained (**Table 2**, entry 4). For other secondary amines, such as 1-methyl-piperazine (**2b**), piperazine (**2c**) and di-*n*-butyl-amine (**2d**), the corresponding products were also obtained in good to excellent yields (**Table 2**, entries 5 - 9). Interestingly, when piperazine (**2c**), which has two reactive -NH sides, was tested with 2 mmol (4 equiv) of **1c**, 35 % of mono *N*-benzylation and 55 % of 1,4-*N*-dibenzylation product was obtained (Supporting information, **Table S2a**, entry 11). With increasing the amount of **1c** to 3 mmol (6 equiv), the 1,4-*N*-dibenzylation product (**3h**) was obtained in 90 % isolated yield (Supporting information, **Table S2a**, entry 12).

Next, secondary benzylic amines, which are less basic compared to secondary aliphatic amines[20], were used as the substrate (**Table 2**). *N*-methyl benzylamine (**2e**) reacted smoothly with **1a**, **1d**, **1g** and the corresponding products were obtained in good to excellent yields (**Table 2**, entries 10 – 12). Similarly the reaction of 1,2,3,4-tetrahydroisoquinoline (**2f**) with alcohols **1a**, **1e**, **1h** provided the corresponding products in high yields (**Table 2**, entries 13 – 15). Remarkably, alcohols, which possess hetero-aromatic moieties such as **1e** and **1h**, which have the possibility to act as chelating ligands, could also be used as shown in various entries in **Table 2**, and products **3e**, **3i**, **3o** and **3p** could be obtained in good to excellent

Table 3. Amination of benzyl alcohols with primary amines.[a]



Entry	Substrate **1**	Product **5**	Yield [%][b]
1	**1b** 	**5a** 	54
2	**1a** 	**5b** 	61
3	**1c** 	**5c** 	59
4	**1g** 	**5d** 	53
5	**1i** 	**5e** 	42
6	**1j** 	**5f** 	22
7	**1c** 	**5g** 	60
8	**1c** 	**5h** 	61
9	**1f** 	**5i** 	60
10	**1a** 	**5j** 	70
11	**1a** 	**5k** 	66
12	**1c** 	**5l** 	56

[a]**General reaction conditions**: **General Procedure** (see Supporting information, page S2), 0.5 mmol **2**, 2 mmol **1a**, 0.02 – 0.03 mmol **Cat 1**, 0.04 - 0.06 mmol Me_3NO, 2 ml solvent, 18 - 24 h, 135 °C, 95 - 105 mg molecular sieves, for specified conditions see Supporting information, **Table S3**. [b]Isolated yields.

yield.[21]

Reactions of benzyl alcohols with primary amines. We recently reported the synthesis of mono-*N*-alkylated benzylamines from the corresponding primary benzylamines and aliphatic alcohols.[18] Here we demonstrate a new alternative route to the same products, starting from benzyl alcohols and aliphatic amines (**Table 3**), which to the best of our knowledge has not been previously reported with any iron catalyst, and allows great synthetic flexibility for the selection of the substrates and more insight into the reaction mechanism.

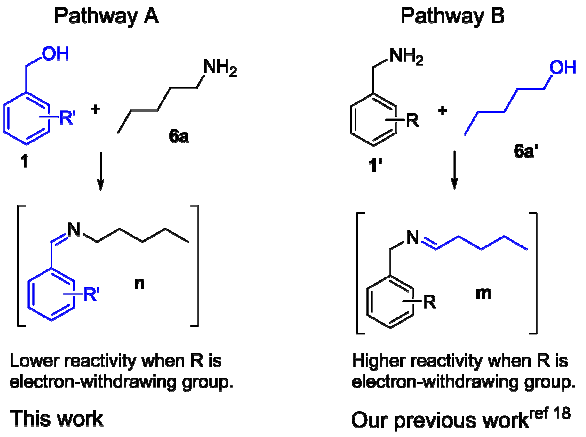
First, *n*-pentylamine (**4a**) was selected for the synthesis of a variety of functionalized benzyl alcohols (**Table 3**, entries 1 – 6; Supporting information, **Table S3**, entries 1 to 13). Selectivity towards the mono-alkylation products was sensitive to the amount of alcohol substrate added. For example, 2 eq. of 4-methoxybenzyl alcohol (**1b**) lead to preferential formation and 54% isolated yield of **5a** (**Table 3**, entry 1; Supporting information, **Table S3**, entry 2), however further increasing **1b** loading lead to more dialkylation product (Supporting information, **Table S-3**, entry 1). On the other hand, only using 1.5 eq of **1b,** the corresponding imine was detected as the major product (Supporting information, **Table S3**, entry 3). The same behavior was observed with 4-methylbenzyl alcohol (**1a**) (Supporting information, **Table S3**, entries 4 - 6). In addition, increasing **Cat 1** loading to 6 mol % provided 61 % isolated yield of **5b** (Supporting information, **Table S3**, entry 2).

Interestingly, when less electron-rich substrates such as benzyl alcohol (**1c**) and 4-fluorobenzyl alcohol (**1g**) were examined, less di-*N*-benzylation product was observed and 59 % and 53 % of mono-*N*-benzylation products were isolated, respectively (**Table 3**, entries 3 and 4).

The reaction of 3-chlorobenzyl alcohol (**1i**) and 3-trifluoromethylbenzyl alcohol (**1j**) with *n*-pentylamine (**4a**) (Supporting information, **Table S3**, entries 9 - 13) was examined as comparison with our previous approach[18] that used 3-chloro and 3-trifluoromethyl substituted benzylamines. In the present case, both reactions provided preferentially imine products (Supporting information, **Table S3**, entry 9 and 12, 13). Increasing the catalyst loading to 6 mol % and reaction time to 24 h, provided more amine product **5e** (Supporting information, **Table S3**, entry 10) but still rather low amounts of desired amine **5f** (31%, Supporting information, **Table S3**, entry 13) were obtained. Increasing the reaction temperature to 140 °C in order to facilitate imine reduction resulted in catalyst decomposition (Supporting information, **Table S3**, entry 11).

In our previous study[18], electron-deficient benzylamines were more reactive towards mono-alkylation than their electron rich analogues. The results shown here, however, conclude that *N*-alkylated benzylamines are more readily obtained starting from electron-rich benzyl alcohols than from electron poor benzyl-alcohols (**Scheme 3**). The reason for this reactivity difference can likely be attributed to

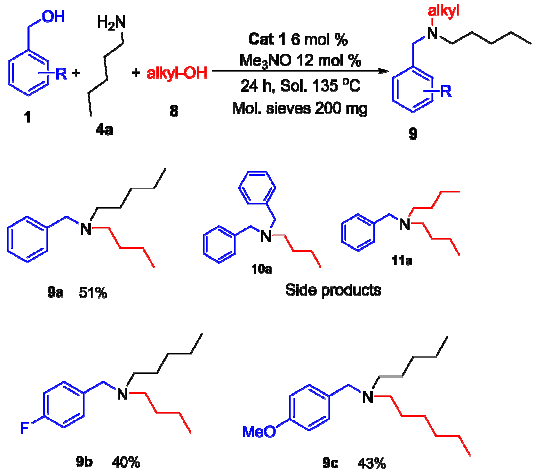
Scheme 3. Reactivity difference through different substrates.



differences in the rate of the imine reduction step.[22] It has to be noted that the imine intermediates formed from benzyl-alcohols will possess a double bond in conjugation with the aromatic system (Pathway A, **Scheme 3**) and those formed from benzyl amines will not (Pathway B, **Scheme 3**). These reactivity differences under similar conditions, also show that isomerization of the imine double bond is not likely. The detailed understanding of these mechanistic details and rate limiting steps will be subject of future in depth-studies.

Next, a series of other primary amines were tested as substrates (**Table 3**, Entry 7 - 12). Long chain amines like *n*-nonylamine (**4b**) and 2-phenylethamine (**4c**) were benzylated with benzyl alcohol (**1c**) providing **5g** and **5h** in good isolated yields (**Table 3**, entries 7 and 8). Furthermore, primary benzylamines and anilines could be readily applied to provide **5k** and **5l** (**Table 3**, entries 9 – 12).

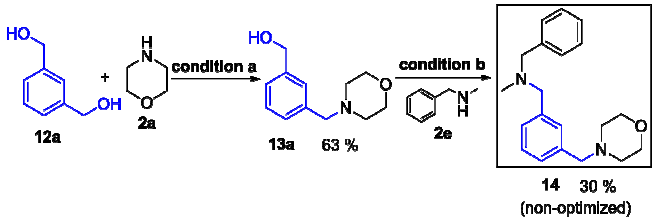
Scheme 4. One pot synthesis of asymmetric benzylic tertiary amines.[a]



[a]**General reaction conditions**: **General Procedure** (see Supporting information, page S2), 0.5 mmol **4a**, 1 or 2 mmol **1**, 1 or 1.5 mmol **8**, 0.03 mmol **Cat 1**, 0.06 mmol Me_3NO, 2 ml solvent, 24 h, 135 °C, 195 - 205 mg molecular sieves,for specified conditions, see Supporting information, **Table S-4**. Isolated yields are shown for each products.

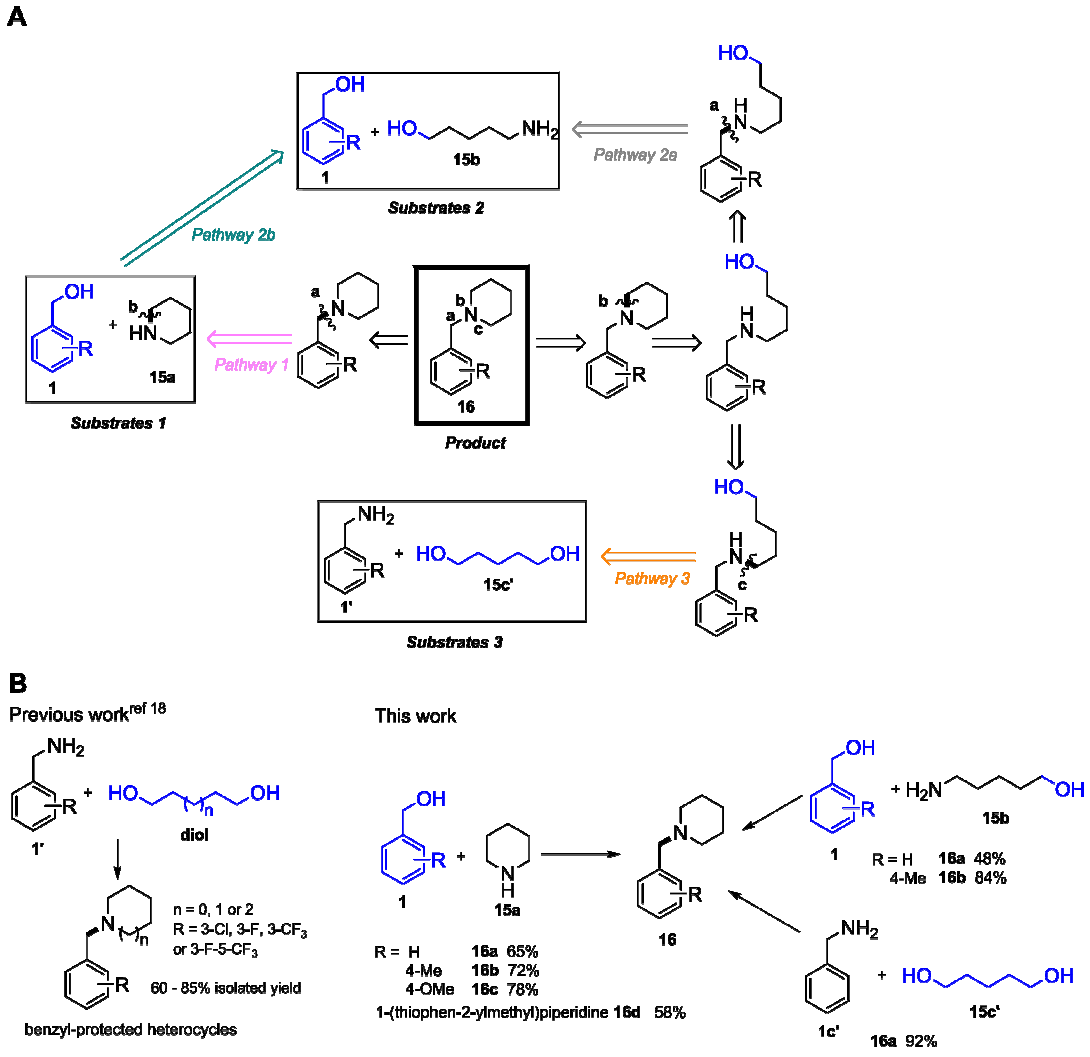
A one-pot method for the preparation of non-symmetric tertiary amines. Taking advantage of the differences in reactivity between aliphatic and benzyl alcohols, we have developed a straightforward approach for the direct one pot synthesis of non-symmetric benzylic tertiary amines (**Scheme 4**). To this end, a method using benzyl alcohol (**1c**), *n*-pentylamine (**4a**) and *n*-butanol (**8a**) was implemented with 6 mol % **Cat 1** loading, at 135 °C. Gratifyingly, the desired non-symmetric *N*-*n*-butyl-*N*-*n*-pentylbenzylamine (**9a**) was predominant in the reaction mixture that also contained smaller amounts of the expected di-*N*-benzyl-*n*-pentylamine (**10a**), and di-N-*n*-butyl-*n*-pentylamine (**11a**) (Supporting information, **Table S4**, entry 1). The desired tertiary amine with three distinctly different alkyl moieties **9a** was isolated in 51 % yield. The one-pot procedure was extended to the synthesis of other non-symmetric tertiary amines **9b** and **9c** (Supporting information, **Table S4**, entries 4 – 6).

Scheme 5. Sequential functionalization of diols.[a]



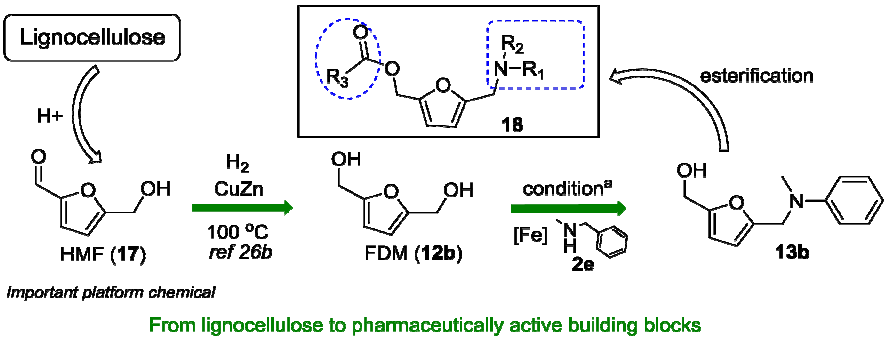
[a]**Condition a**: **General Procedure** (see page S2), 0.5 mmol **2a**, 1.5 mmol **12a,** 0.02 mmol **Cat 1**, 0.04 mmol Me_3NO, 135 °C, 2 ml toluene, 18 h, 95 - 105 mg molecular sieves. 63 % of **13a** was isolated. **Condition b**: **General Procedure** (see page S2), 0.5 mmol **2e**, 1 mmol **13a,** 0.03 mmol **Cat 1**, 0.06 mmol Me_3NO, 135 °C, 2 ml toluene, 18 h, 95 - 105 mg molecular sieves. 30 % of **14** was isolated.

Scheme 6. Retro-synthetic analysis and diverse approaches for synthesizing *N*-benzyl piperidines.[a]



[a]**A.** Retro-synthesis analysis of *N*-benzyl piperidines. **B.** Diverse approaches for synthesizing *N*-benzyl piperidines. **General reaction conditions**: **General Procedure** (see Supporting information, page S2), 0.5 or 1 mmol **15**, 0.5 or 2 mmol **1,** 0.02 mmol **Cat 1**, 0.04 mmol Me_3NO, 135 °C, 2 ml toluene, 18 or 24 h, 95 - 105 mg molecular sieves, for specified conditions see Supporting information, **Table S5**. Isolated yields are shown for each products.

Scheme 7. Synthesis of key intermediate to muscarinic agonist, *N*-[5-([l'-substituted-acetoxy)methyl]-2-furfurylldialkylamines.



[a]**General Procedure** (see page S2), 0.5 mmol **2e**, 2 mmol **12b,** 0.02 mmol **Cat 1**, 0.04 mmol Me_3NO, 135 °C, 2 ml toluene, 24 h, 95 - 105 mg molecular sieves. 60 % of **13b** was isolated.

Sequential functionalization of diols to obtain diverse diamines. Sequential functionalization of diols is undoubtedly a valuable synthetic tool to obtain compounds with great diversity. Here we present, for the first time, a selective iron catalysed method that allows for the preparation a non-symmetric functionalized diamines. This reaction sequence was demonstrated for the preparation of compound **14** whereby diol **12a** was selectively monoalkylated with **2a** forming **13a.** This was followed by amination of **13a** with **2e** to provide **14**. (**Scheme 5**)

Diverse approaches to N-benzyl piperidines. *N*-hetercycles are compounds of major interest due to their prominent role in bio-active compounds *e.g*. pharmaceuticals and agrochemicals.[23] Our previous study showed the direct synthesis of benzyl-protected five, six, and seven membered-heterocycles from benzylamines and diols.[18]

Here, we have investigated versatile synthesis routes for the preparation of *N*-benyzl piperidine as representative example for benzyl protected N-heterocycles (illustrated in **Scheme 6**). The same *N*-benyzl piperidine **16** can be obtained *via* three distinct routes, starting from different substrates (**Scheme 6**). For example, **16** can be synthesized from three sets of substrates through four pathways (**Scheme 6**, **A**). **16** can be obtained from benzyl alcohol (**1**) and piperidine (**15a**) through the formation of bond **a** (**Scheme 6**, **A**, *Pathway 1*). Alternatively, **16** can be obtained from **1** and 5-amino-1-pentanol (**15b**) through the sequential formation of bonds **a** and **b** (**Scheme 6**, **A**, *Pathway 2a*), or **b** and **a** (**Scheme 6**, **A**, *Pathway 2b*). Also, **16** can be synthesized starting from 1,5-pentanediol (**15c'**) and **1c'** during which bonds **b** and **c** are formed (**Scheme 6**, **A**, *Pathway 3*). These substrate variations allow for choosing the most suitable pathway[24] taking into account optimal balance of reactivity, selectivity and substrate abundance. In order to show the power of this method, **16a**, **16b**, **16c**, and **16d** were synthesized through different pathways, with good to excellent yields (**Scheme 6**, **B**).

From cellulose derived platform chemicals to pharmaceutically active molecules. It was reported that furanic compounds of the general structure (**18**) shown on **Scheme 7** are a class of pharmaceutically active compounds possessing potential antimuscarinic activity. Pharmaceutical studies have especially focused on systematic modifications of the ester- and amine side chains.[25] Here we show an efficient and fully sustainable synthetic strategy towards obtaining key intermediate **13b.** This compound can be prepared directly from benzyl amine derivative **2e** and diol **12b** using our iron catalysed methodology. Diol **12b** used in this reaction can be obtained in high yield from 5-(hydroxymethyl)furfural (HMF, **17**), via a sustainable pathway we have recently reported[26]. In this procedure, HMF, which is one of the most important cellulose derived platform chemicals undergoes catalytic hydrogenation using robust, CuZn alloy nanopowder catalysts[26b]. This novel combination of methods allows for the easy, waste free synthesis of key bioactive intermediate **13b** from renewable resources, using sustainable catalysis.

CONCLUSION

In conclusion, we have established, for the first time, a general methodology for the catalytic formation of value-added benzylamines through amination of benzylalcohols using a well-defined iron catalyst that operates through a hydrogen borrowing mechanism. Many synthetically challenging routes were systematically explored starting from readily accessible substrates that do not require prior alcohol activation by stoichiometric methods. This included the one-pot synthesis of asymmetric tertiary amines, the sequential functionalization of diols as well as the synthesis of important synthons, for example, N-benzyl-piperidines through diverse synthetic pathways. In addition, direct conversion of renewable building block 2,5 furan dimethanol to pharmaceutically relevant compounds was achieved with unprecedented simplicity. Future work focuses on elucidating mechanistic questions and the design of new catalyst structures.

EXPERIMENTAL SECTION

Reagents and Characterization Methods Reagents were of commercial grade and used as received, unless stated otherwise. Complex **Cat 1** was synthetized according to literature procedures[27]. Chromatography: Merck

silica gel type 9385 230-400 mesh or Merck Al_2O_3 90 active neutral, TLC: Merck silica gel 60, 0.25 mm or Al_2O_3 60 F254 neutral. Components were visualized by UV, Ninhydrin or I_2 staining. ^{1}H- and ^{13}C NMR spectra were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using $CDCl_3$, CD_3OD, or CD_2Cl_2 as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 for ^{1}H, 77.00 for ^{13}C; CD_3OD: 3.31 for ^{1}H, 49.00 for ^{13}C; CD_2Cl_2: 5.32 for ^{1}H, 53.84 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants (Hz), and integration.

Representative Procedures Procedure of amination of 4-methoxybenzyl alcohol (**1b**) with morpholine (**2a**) provides **3b**: An oven-dried 20 ml Schlenk tube, equipped with stirring bar, was charged with 4-methoxybenzyl alcohol (2 mmol, 0.276 g), iron complex **Cat 1** (4 mol %, 8 mg) and Me_3NO (8 mol %, 3 mg) under air. Then the Schlenk tube was subsequently connected to an argon line and a vacuum-argon exchange was performed three times. Morpholine (0.5 mmol, 0.044 g), and toluene (solvent, 2 ml) were charged under an argon stream followed by addition of 95 – 105 mg activated molecular sieves 4A. The Schlenk tube was capped and the mixture was rapidly stirred at room temperature for 1 min, then was placed into a pre-heated oil bath at 135 °C and stirred for 18 h. The reaction mixture was cooled down to room temperature and the crude mixture was filtered through celite, eluted with ethyl acetate, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/EtOAc 80:20 to 50:50) to provide the pure amine product **3b** (0.091 g, 88 % isolated yield). For characterization data, see the Supporting information.

ASSOCIATED CONTENT

Supporting Information.

Experimental details and NMR spectra (^{1}H, ^{13}C), HRMS, of all reaction products are include in the supporting information. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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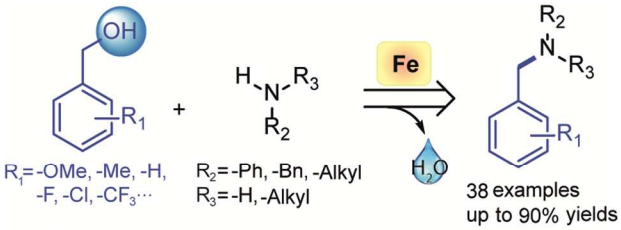

-Systematic scope
-Reactivity insight
-Applications in sythesis