From Wood to Tetrahydro-2-benzazepines in Three Waste-Free Steps: Modular Synthesis of Biologically Active Lignin-Derived Scaffolds

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Supporting Information

ABSTRACT: Inherently complex, lignin-derived aromatic monomers comprising valuable structural moieties present in many pharmaceuticals would serve as ideal substrates for the construction of biologically active molecules. Here, we describe a strategy that incorporates all intrinsic functional groups present in platform chemicals obtained by lignin depolymerization into value-added amines, using sustainable catalytic methods and benign solvents. Our strikingly efficient protocol provides access to libraries of aminoalkyl-phenol derivatives and seven-membered N-heterocycles directly from wood in two, respectively three, waste-free steps. Several molecules in these libraries have shown promising antibacterial or anticancer activities, emphasizing the advantage of this modular synthetic strategy and the potential for drug discovery. The sustainable catalytic pathways presented here can lead to significant benefits for the pharmaceutical industry where reduction of hazardous waste is a prime concern, and the described strategies that lead to high-value products from non-edible biomass waste streams also markedly increase the economic feasibility of lignocellulosic biorefineries.

INTRODUCTION

Inherently complex renewable building blocks offer marvelous opportunities for the construction of biologically active target molecules through entirely waste-free pathways.1-3 Achieving such atom-economic routes represents one of the most essential goals in the pharmaceutical industry, where reduction of E-factors is crucially important.4,5

Because of its naturally occurring functionalized aromatic moieties6,7 omnipresent in biologically active compounds,8 the abundant biopolymer lignin would serve as excellent starting material for the development of such innovative routes.

Mild lignin depolymerization has attracted significant attention in recent years.9 Elegant strategies have emerged, which provide access to well-defined aromatic platform chemicals in near-theoretical yields.10-14 The next grand challenge in lignin refining is the diversification of these newly emerging building blocks to access industrially relevant products and concrete applications.15 While much research has focused on polymers16,17 or bulk chemicals,9,10 surprisingly only one example18 and no waste-free methods have been reported for the transformation of these aromatics to fine chemicals or pharmaceutical building blocks.

The platform chemicals originating from the most prominent mild depolymerization methods maintain, at least partly, the complexity of the parent lignin (Figure 1a).3 Thus, transforming these to bulk chemicals (e.g., phenol, catechol, or BTX) necessitates further defunctionalization steps via energy-intensive C=O and C=C bond cleavage reactions.19 In contrast, when targeting pharmaceutically relevant compounds,
the whole array of intrinsic functionality available in these platform chemicals could be utilized. In this contribution, we describe such unprecedented routes for the construction of valuable but synthetically challenging seven-membered N-heterocyclic target molecules.8

Benzazepine derivatives20 are prominent pharmaceutically relevant compounds, conventionally synthesized in multiple steps that generally suffer from the production of stoichiometric amounts of waste (Figure 1b); for analysis of representative examples, see Supplementary Section 2). Taking advantage of the inherent phenylpropanoid moieties of relevant platform chemicals, we here provide access to tetrahydro-2-benzazepines in three highly selective steps directly from renewable lignocellulose while using green solvents or alternative reaction media and not producing any byproduct except for water.

This novel method consists of (a) the catalytic amination of dihydroconiferyl (1G) and dihydrosinapyl alcohol (1S) obtained from lignocellulose by means of our previously developed “LignoFlex”2 process and (b) the construction of seven-membered N-heterocycles using deep eutectic solvents (DES)21 that consist solely of natural components.22,23 The former step takes place in the nontoxic solvent CPME and allows for obtaining valuable N-alkyl-amine derivatives directly from 1G (and 1S), contained in crude lignin-first depolymerization mixtures, by a new reactive separation strategy. The latter step uses benign, biodegradable, and recyclable alternative reaction media acting both as a catalyst and a solvent, leading to improved activity and selectivity, milder reaction conditions, and rendering strong acids or any other additives obsolete.

This highly modular approach allows access to a library of tetrahydro-2-benzazepines, which were evaluated in terms of their antibacterial or anticancer activity. Several scaffolds have shown promising biological activities emphasizing the advant-

Figure 1. Tetrahydro-2-benzazepine derivatives from petrochemicals versus renewable resources. (a) Conversion of lignin-derived platform molecules to bulk chemicals versus biologically active compounds: a comparison of low atom-economy defunctionalization strategies (established) and using all inherent functionality (this work). (b) Conventional, multistep syntheses for the construction of tetrahydro-2-benzazepines and their disadvantages (a detailed description of routes is shown in Supplementary Section 2.3). (c) Pharmaceutically relevant compounds containing a benzazepine moiety. (d) The overall strategy of this work: Sustainable construction of lignin-derived tetrahydro-2-benzazepines. From lignocellulose to seven-membered N-heterocycles in three waste-free steps. Step 1: Reductive catalytic fractionation (RCF) of lignocellulose to deliver a crude depolymerization mixture, including lignin-derived platform chemical 1G. Step 2: Highly selective Ru-catalyzed amination of the platform chemical 1G via the borrowing-hydrogen strategy, involving reactive separation of 1G from the crude RCF mixture. Step 3: Pictet–Spengler cyclization of the obtained secondary amines in deep eutectic solvents (DES) that are nontoxic and can be derived from renewables.
RESULTS AND DISCUSSION

Highly Efficient Amination of Lignin-Derived Alcohols. Recently, we have developed the flexible use of copper-doped porous metal oxides (Cu20-PMO) for the full conversion of lignocellulose to valuable aromatics and fuels (LignoFlex).2 The reductive catalytic fractionation step of this method resulted in aromatic monomers, predominantly dihydroconiferyl alcohol 1G (>90% selectivity from pine) as well as smaller amounts of 4-ethylguaiacol (2G) and 4-propylguaiacol (3G).

Further in-depth analysis herein revealed that besides 1G, 2G, and 3G, the depolymerization mixtures also contained residual sugars and lignin oligomers (see Supplementary Section 4.1). The isolation and purification of single aromatic compounds from lignin or “lignin-first” depolymerization mixtures are a common challenge in the field. Therefore, our aim here was to accomplish the reactive separation of 1G by its one-step conversion to valuable amines—that have not yet been accessed from lignin—directly in crude product mixtures obtained from reductive depolymerization of pine and poplar lignocellulose (see Supplementary Section 4). Thus, we focused on providing a novel and waste-free amination protocol, involving the aliphatic alcohol moiety of 1G and 1S. To this end, the development of a robust catalytic method that tolerates the multicomponent crude depolymerization mixture and is selective enough to allow for good separation while maintaining a high enough renewable carbon balance was deemed necessary. Notably, while coupling of alcohols and amines via the borrowing-hydrogen methodology has been widely studied,24,25 this approach has been only scarcely applied to lignin-derived aromatics comprising a free phenol moiety. Such scaffolds may coordinate to transition metal species or interfere with the strong base, critical for these methods.

Previously, we found that Shvo’s catalyst (C1) is active in the base-free N-alkylation of potentially strongly coordinating unprotected amino acids with alcohols.26 Therefore, C1 was

Table 1. Establishing the Highly Selective Catalytic Amination of Dihydroconiferyl Alcohol 1G

| entry | changes | yield (%)
|-------|--------|---------|
| 1     | as above | >99 (75) |
| 2     | C1 (0.5 mol %) | 33 |
| 3     | 100 °C | 42 |
| 4     | 1 equiv. of 1G | 93 |
| 5     | 8 h | 52 |
| 6     | no C1 | 0 |
| 7c    | 4-chloroaniline (4b) instead of aniline | >99 (97) |
| 8d    | 4b | >99 (94) |

All the reactions were run with 4a (0.25 mmol) and 1G (0.3 mmol). Yield was determined by GC-FID (isolated yield). 4b (0.4 mmol), 1G (0.48 mmol), CPME (2 mL). 4b (5.95 mmol), 1G (7.14 mmol), CPME (20 mL).

Figure 2. A reactive separation protocol to obtain biobased amines directly from crude RCF mixtures of pine lignocellulose. Description of the depolymerization and reactive separation strategy. (a) Reductive catalytic fractionation (RCF) of pine lignocellulose using Cu20-PMO to deliver a crude depolymerization mixture. (b) Fractionation of the crude depolymerization mixture with ethyl acetate (EtOAc) to eliminate high Mw lignin residues. (c) Method 1: Ru-catalyzed amination of 1G in Fraction 1. (d) Method 2: Ru-catalyzed amination of 1G directly in crude RCF mixture. More details of reactive separation are shown in Supplementary Section 4.
evaluated in the catalytic amination of 1G with aniline (Table 1, and Supplementary Table 2). The desired secondary amine 5Ga was obtained in perfect selectivity (99%) and good isolated yield (75%) using the nontoxic solvent CPME and 1 mol % C1 without any additives (Table 1, Entry 1). Appropriate blank reactions showed no product formation and a mercury-poisoning experiment confirmed the homogeneous nature of the catalytic system. An even better 97% isolated yield of 5Gb was obtained using 4-chloroaniline 4b as a coupling partner (Table 1, Entry 7). This reaction could also be upscaled using 1.3 g of 1G to deliver a 94% isolated yield of 5Gb, important for establishing the reactive separation method (Table 1, Entry 8).

**Reactive Separation from Lignocellulose Depolymerization Mixtures.** Having this remarkably selective method in hand, we set out to establish the desired reactive separation protocol first with simple model compound mixtures consisting of 1G and 3G in various ratios (1:1 and 1:3) using p-chloroaniline (4b) as the amine substrate (Supplementary Section 4.2). The varying amount of 3G besides 1G did not have a detrimental effect on the reaction efficiency, and the amine 5Gb could be obtained in 85% isolated yield (Supplementary Table 3). Next, we generated product mixtures by depolymerization of pine and poplar lignocellulose over Cu20-PMO and 40 bar H2 and performed their analyses with multiple methods (Supplementary Sections 4.1 and 4.2). Fractionation of the obtained crude was carried out using ethyl acetate for the easy separation of higher molecular weight lignin as a brown solid residue (Supplementary Figures 10 and 15). Then, the colorless ethyl acetate-soluble fraction, containing 1G and other components, was subjected to the amination protocol (5 mol % C1) with 2 equiv. of 4b, furnishing the desired secondary amine 5Gb in 84% isolated yield (Supplementary Section 4.3.1). It is worthwhile to note that the amination of multicomponent Fraction 1 (Figure 2, Supplementary Section 4.3) required slightly higher loading of C1 and 4b than the standard protocol established for pure 1G (Table 1). In order to verify the influence of the various components present in Fraction 1 on reactivity, the catalytic amination of 1G was conducted in the presence of different additives. Indeed, these experiments confirmed that glucose and a typical lignin β-O-4 model comprising both a primary and secondary aliphatic alcohol moiety slightly affected the amination reaction at 1 mol % C1 loading, while lignin oligomers with low β-O-4 content had no effect on the outcome of this reaction (see Supplementary Note 1 for a detailed discussion). The functionalization of 1G was also successfully carried out in the crude lignin-first depolymerization mixture directly (Figure 2). This required solvent exchange from methanol to CPME, and increasing the catalyst loading to 10 mol % and 4b amount to 4 equiv. We attribute the need for these increased C1 and 4b amounts to the presence of high Mw lignin and sugar oligomers (previously removed as Fraction 2, Supplementary Note 1) present in the...
phenolic analogues. Interestingly, anilines potentially serve as NO donor similarly to already described products obtained, valuing in the treatment of Alzheimer and tris-dihydroxyaryl analogues have been shown to be crude. Under these conditions, the desired $5G_b$ (39 mg) was obtained in 64% isolated yield, and the unreacted $2G$ and $3G$ could also be easily separated (Supplementary Section 4.3.2).

Similar considerations applied for the reactive separation of depolymerization mixtures from poplar lignocellulose, which contain both $1G$ and $1S$ in higher quantities (Supplementary Section 4.5.1). Amination of $1G$ and $1S$ residing in the ethyl acetate-soluble fraction with $p$-chloroaniline ($4b$) resulted in the desired products $5G_b$ and $5S_b$ in 72% and 56% isolated yield, respectively. Direct catalytic amination using the crude mixture obtained from poplar wood gave 57% of $5G_b$ and 45% of $5S_b$ (Supplementary Section 4.5.2).

**Amino Alkyl-phenol Derivatives from Lignin Monomers.** In order to provide straightforward access to a library of novel lignin-based amino alkyl- and aryl-guaiacols, the modular coupling of $1G$ with (hetero)aromatic and aliphatic primary amines as well as secondary amines was successfullly carried out using the developed Ru-catalyzed methodology (Table 2). Anilines $4b$–$4i$ carrying electron-withdrawing and -donating groups were selectively monoaalkylated to form the corresponding secondary amine products $5G_b$–$5G_i$ in good to outstanding isolated yields. Interestingly, excellent functional group tolerance was observed with the sulfur-containing $4h$ as well as with anilines containing reducible functional groups $-\text{NO}_2$, $-\text{CN}$, $-\text{COOH}$, $\text{COCH}_3$, and an alkene. Among the products obtained, $5G_j$ containing a $p$-nitroaniline moiety may potentially serve as NO donor similarly to already described phenolic analogues.\(^\text{27}\) Interestingly, anilines $4o$ and $4p$ gave 61% $5G_o$ and 81% $5G_p$, respectively. Previously, several bis- and tris-dihydroxyaryl analogues have been shown to be valuable in the treatment of Alzheimer’s disease, type-II diabetes, and Parkinson’s disease.\(^\text{26}\) Moreover, $5G_p$ could serve as a novel sustainable bisphenol for the synthesis of biobased polymers.\(^\text{29}\) Furthermore, $5G_q$, $5G_r$, and $5G_s$ were isolated in good to moderate yields (81%, 53%, and 55% respectively). When secondary amines $4t$, $4u$, and $4v$ were used as coupling partner, the corresponding tertiary amines $5G_t$, $5G_u$, and $5G_v$ were obtained in good yield. These may serve as starting materials for the synthesis of pharmaceutically active compounds, primarily upon quaternarization.\(^\text{30,51}\)

Primary amine, 3-aminopropyl guaiacol ($5G_w$) was considered as an important target that can be subjected to further derivatization. Despite several attempts, we were unable to obtain $5G_w$ from ammonia and $1G$ using the studied Ru-catalyzed coupling (Supplementary Table 7). Therefore, a novel methodology was developed that uses a commercially available Raney nickel catalyst and easy to handle aqueous ammonia to deliver primary amine $5G_w$ as HCl salt in 46% isolated yield (Supplementary Figure 32).

The reactivity of $1S$ that can be obtained from poplar lignocellulose in larger quantities was found to be very similar to that of $1G$; thus, a library of amino alkyl-syringols was created smoothly with excellent functional group tolerance observed (Table 3).

**Construction of Seven-Membered N-Heterocycles in Deep Eutectic Solvents.** Benzazepine derivatives are a prominent class of compounds in the pharmaceutical industry (e.g., diazepam \(^\text{32}\)). In particular, tetrahydro-2-benzazepines have shown promising biological activities.\(^\text{34–36}\) This scaffold is present in important naturally occurring alkaloids\(^\text{37}\) including galanthamine,\(^\text{38}\) a very effective drug for the treatment of Alzheimer’s disease. Furthermore, capsazepine and its derivatives have been widely investigated as selective antagonists of vanilloid type-1 receptors.\(^\text{39}\) Because of these valuable pharmacological properties, the synthesis of tetrahydro-2-benzazepines has been extensively studied.\(^\text{40–41}\) Taking advantage of the inherent phenylpropanoid moiety of lignin-derived $1G$, our aim was to develop a new sustainable method that would represent a significant improvement over conventional synthetic routes (Supplementary Section 2.3 for description of stoichiometric routes). Given the importance of the Pictet–Spengler reaction in the synthesis of alkaloid...
Table 4. Construction of Lignin-Derived Tetrahydro-2-benzazepines in Deep Eutectic Solvent Comprising Choline Chloride/Oxalic Acid

![Chemical Structures]

| Compound | Reaction Conditions | Isolated Yield |
|----------|--------------------|----------------|
| 5Gb      | ChCl/OA (1 g)      | 87%            |
| 6Gb      | ChCl/OA (1 g)      | 82%            |
| 6Gc      | ChCl/OA (1 g)      | 63%            |
| 6Gd      | ChCl/OA (1 g)      | 51%            |
| 6Ge      | ChCl/OA (1 g)      | 91%            |
| 6Gf      | ChCl/OA (1 g)      | 61%            |
| 6Gg      | ChCl/OA (1 g)      | 71%            |
| 6Gh      | ChCl/OA (1 g)      | 59%            |
| 6Gi      | ChCl/OA (1 g)      | 70%            |
| 6Gj      | ChCl/OA (1 g)      | 95%            |
| 6Gk      | ChCl/OA (1 g)      | 83%            |
| 6Gl      | ChCl/OA (1 g)      | 66%            |
| 6Gm      | ChCl/OA (1 g)      | 41%            |
| 6Gn      | ChCl/OA (1 g)      | 4%             |
| 6Go      | ChCl/OA (1 g)      | 86%            |
| 6Gp      | ChCl/OA (1 g)      | 4%             |
| 6Gq      | ChCl/OA (1 g)      | 8%             |

General reaction conditions: 5G or 5S (0.150–0.366 mmol), ChCl/OA (1 g), 70–80 °C, 20–48 h. Isolated yields are shown. We carried out all the cyclization experiments under noninert conditions during which all starting materials and solvents were handled under air.

scaffolds, and in particular, its use for the cyclization of 3-arylpropylsulfonamides with formaldehyde to construct N-sulfonyl-2-benzazepines, we attempted to realize the green synthesis of novel seven-membered N-heterocycles via this method, starting from the library of amines obtained by clean catalytic transformation of 1G and 1S (Tables 2–3). Adapting conventional protocols, we performed cyclization using 5Gb as a model substrate and paraformaldehyde in various organic solvents screening Brønsted and Lewis acid catalysts. This led to only moderate success due to competing methylation of the alkyl-amine substrates that prevented efficient cyclization, and the formation of regioisomers was also observed (Supplementary Section 6.1). In order to markedly improve selectivity and efficiency, we have turned our attention to the use of deep eutectic solvents (DES) for the first time for the formation of tetrahydro-2-benzazepines. Because of their favorable properties such as excellent solvent power, negligible vapor pressure, and good recyclability, DES have demonstrated enormous potential as a sustainable and benign replacement of common organic solvents in various applications, including organic synthesis. The highly ionic nature and strong hydrogen-bond donor properties of several DES have already been shown to be beneficial for facilitating classical organic transformations (e.g., those involving activation of a carbonyl compound). One example of a Pictet–Spengler cyclization using the specific substrate tryptamine has been reported in a choline chloride (ChCl)/urea DES. However, the same DES turned out to be unsuitable for the formation of the desired tetrahydroisoquinoline using 3,4-dimethoxy-phenyl ethylamine, only leading to the corresponding imine intermediate. Inspired by this system, we reasoned that besides the excellent hydrogen-bond acceptor, choline chloride (ChCl), an organic acid component (lactic acid (LA) or oxalic acid (OA)) would be highly suitable for facilitating the required carbonyl-activation and proton-transfer events involved in the iminium formation and subsequent Mannich-type cyclization steps. Advantageously, such DES comprises solely natural components, which are nontoxic, biodegradable, and potentially bioderived.

To our delight, the combination ChCl/OA showed full conversion of 5Gb and very good selectivity of the desired cyclization product 6Gb under mild reaction conditions (70 °C) without the need for any strong acids or other additives (Supplementary Section 6.2). Notably, good results...
were achieved even at temperatures as low as 50 °C and 8 h reaction time. Next, we explored the desired cyclizations with several alkyl amines in hand under optimized reaction conditions (Table 4). The seven-membered N-heterocyclic products were obtained in outstanding selectivity and good to excellent isolated yields (Supplementary Table 10).

**Evaluation of Biological Activity.** In order to identify possible biological effects of our compounds, we evaluated their potential anti-infective activity toward representative Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria. In parallel, we determined their effects on a human hepatoma cell line (Hep G2) as an early indication of anticancer activity. While the compounds were inactive against *E. coli* K12, promising activities were observed against *S. aureus* (Figure 3), where the best compounds reached MIC values between 40 and 50 μM (Supplementary Table 11). If these values are compared with erythromycin, an antibiotic that is therapeutically used to treat this pathogen and utilized in this study as a reference compound, we observe an about 10-fold higher MIC for the best lignin-derived inhibitor 6Ge. Since our compounds have not yet been optimized in this respect, this difference seems to be acceptable. Interestingly, as the activities of four selected compounds were much more pronounced in the efflux-pump-deficient *E. coli* TolC strain (Supplementary Table 12), the lack of activity against *E. coli* K12 might be due to compound efflux. Besides, also in *E. coli* TolC the MIC of 6Ge was only slightly (~5.5-fold) higher than that of the reference compound chloramphenicol. Furthermore, 14 out of the 41 tested compounds inhibited the viability of HepG2 cells by >85% at 100 μM (Figure 3) with IC<sub>50</sub> values ranging from 30 to 50 μM for the best inhibitors (Supplementary Table 13). In detail, the IC<sub>50</sub> value of the best inhibitor 5Gt (30.4 ± 0.4 μM) was worse than that of the reference compound doxorubicin, but also here, the activity gap (44-fold) should be overcome during medicinal-chemistry optimization.

Analysis of the structure–activity relationships of each of the four classes of compounds revealed interesting common trends. Weakly electron-withdrawing substituents such as the halogens led to the highest cytotoxicities (e.g., 5Gb–e; 5Sb, 5Sc, 5Se; 6Gb, 6Gc, 6Ge; 6Sb, 6Se), whereas strongly deactivating substituents such as p-NO<sub>2</sub> (e.g., 5Gj) caused a decreased cytotoxicity. This decrease may also be ascribed to the increased steric demand of the substituents in question. When considering classes 5G and 5S, N-alkylation appears to be favorable for cytotoxicity (e.g., 5Gt or 5St) for the N-ethylated derivative. Replacement of the N-phenyl substituent by a heterocycle (5Gs) or p-substitution with a pyrrole heterocycle (5Gr) also leads to high cytotoxicity. The most promising antibacterial activities against *S. aureus* were...
observed for 6G and 6S compounds, in particular, for the p-brominated derivatives (6Gc, 6Ge, 6Sc) as well as for the p-chlorinated analogue 6Sb. For class 5, the antibacterial activity against *S. aureus* was weaker than for class 6. In class 5S, compounds 5Sc and 5Sc stood out, featuring p-halogen substituents. The pyrene-derivative 5Gq is the only representative of class 5G that showed significant antibacterial activity.

Taken together, these moderate but promising activities of the novel lignin-derived scaffolds reported here will pave the way for the further optimization and development of the most promising inhibitors toward anticancer drugs and anti-infectives. A viable modification strategy would be to optimize and grow the fragments identified by introducing appropriate substituents, preferably by straightforward catalytic modification of reactive functional groups present in the obtained tetrahydro-2-benzazepines.

## OUTLOOK

The development of fundamentally new, sustainable catalytic methods for constructing pharmaceutical intermediates or biologically active molecules from nonedible renewable resources is highly desired since such high-value molecules would significantly enhance the overall economic feasibility of a lignocellulosic biorefinery and at the same time provide “green” routes for the manufacture of pharmaceuticals.1 In this contribution, we have achieved a very efficient protocol that provides access to seven-membered N-heterocycles from lignin depolymerization mixtures without the formation of any byproducts besides water. This catalytic strategy uniquely incorporates all the intrinsic functional groups of the lignin-derived building blocks 1G and 1S into pharmacologically relevant compounds. The viability of this greatly modular protocol has been demonstrated by the discovery of biologically active structures in the obtained compound library. The short and convenient synthetic route is a key asset for the preparation of derivatives required for multiparameter optimization of hits toward novel therapeutic agents.

Lignin biosynthesis starts from the aromatic amino acids L-phenylalanine and L-tyrosine. It is interesting to note that nature uses the same amino acids to generate a number of pharmacologically relevant natural products by divergent biosynthetic pathways. Consequently, these biologically active compounds, for example, members of the L-dopamine family, as well as six- and seven-membered N-heterocyclic alkaloids comprise similar structural characteristics to the three basic monolignols (p-coumaryl, coniferyl, and sinapyl alcohol) from which lignin is created.

Thus, a chemocatalytic strategy that aims to explore lignin-derived platform chemicals—also structurally related to the monolignols—as templates for the design of synthetic routes to access not only already known structures, but also new structures, has significant potential for the discovery and optimization of biologically active compounds inspired by and derived from nature.

## METHODS

### General Procedure for Ru-Catalyzed Selective Amination of 1G and 1S

An oven-dried 20 mL Schlenk tube, equipped with a stirring bar, was charged with amine (0.4 mmol, 1 equiv.), 1G or 1S (0.48 mmol, 1.2 equiv.), C1 (0.004 mmol, 1 mol %), and cyclopentyl methyl ether (CPME, 2 mL). Solid materials were weighed into the Schlenk tube under air. The Schlenk tube was subsequently connected to an argon line, and vacuum–argon exchange was performed three times. Liquid starting materials and solvent were charged under an argon stream. The Schlenk tube was capped, and the mixture was rapidly stirred at room temperature for 1 min, placed into a preheated oil bath at 130 °C, and stirred for 20 h. The reaction mixture was cooled down to room temperature, and the crude mixture was filtered through silica gel, eluted with ethyl acetate (10 mL), and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography using ethyl acetate/pentane as the eluent.

**General Procedure for Tetrahydro-2-benzazepine Synthesis.** An oven-dried vial equipped with a stirring bar was charged with amino alkyl-phenol (0.150–0.366 mmol, 1 equiv.), paraformaldehyde (0.150–0.366 mmol, 1 equiv.), and CHCl/C6H12O2:H2O (1:1 molar ratio, 1 g) under air. Then the vial was capped, and the mixture was rapidly stirred at room temperature for 1 min and then was heated to 70–80 °C and stirred for 20–48 h. The reaction mixture was cooled down to room temperature, water (2 mL) and saturated solution of NaHCO3 (2 mL) were added, and the reaction mixture was stirred at room temperature for 1 h. The crude mixture was extracted with ethyl acetate (3 × 10 mL), and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography using ethyl acetate/pentane as the eluent.

**Representative Procedure for the Synthesis of 4-(3-Aminopropyl)-2-methoxyphenol (5Gw).** A 10 mL Swage-lok stainless steel microreactor equipped with a stirring bar was charged with substrate 1G (0.5 mmol), Raney Ni (200 mg), aqueous ammonia (0.4 mL, 25%), and t-amyl alcohol (3 mL). Then, the reactor was sealed and placed in a preheated aluminum heating block at 180 °C. After 24 h, the microreactor was cooled down to room temperature using an ice–water bath. The crude mixture was separated from the catalyst by filtration, concentrated *in vacuo*, and diethyl ether (25 mL) and HCl (0.5 mL, 1 M) in diethyl ether were added. A precipitate formed immediately, and the HCl salt was isolated by filtration and washed with diethyl ether (2 × 10 mL). The pure amine product was isolated as a HCl salt.

**Safety Statement.** No unexpected or unusually high safety hazards were encountered.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.9b00781.

Experimental procedures, detailed description for the catalytic N-allylation of 1G, as well as syntheses of tetrahydro-2-benzazepines in common organic and deep eutectic solvents, experiments related to lignocellulose including reactive separation methods, testing of biological activities of the obtained lignin-derived amines, characterization of compounds, and spectral details of isolated compounds (PDF)

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REFERENCES

(1) Shi, Y.; Kamer, P. C. J.; Cole-Hamilton, D. J. Synthesis of pharmaceutical drugs from cardanol derived from cashew nut shell liquid. Green Chem. 2019, 21, 1043–1053.
(2) Sun, Z.; Bottari, G.; Afanasenko, A.; Stuart, M. C. A.; Deuss, P. J.; Frölich, B.; Barta, K. Complete ligninocellulose conversion with integrated catalyst recycling yielding valuable aromatics and fuels. Nat. Catal. 2018, 1, 82–92.
(3) Sun, Z.; Barta, K. Clean and coupled: toward fully sustainable catalytic conversion of lignocellulose to value added building blocks and fuels. Chem. Commun. 2018, 54, 7725–7745.
(4) Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; Richardson, P.; Roschangar, F.; Steven, A.; Welberth, F. J. Key Green Chemistry research areas from a pharmaceutical manufacturers’ perspective revisited. Green Chem. 2018, 20, 5082–5103.
(5) Poliaikoff, M.; Licence, P. Green chemistry. Nature 2007, 450, 810–812.
(6) vanholme, R.; Demedts, B.; Morreel, K.; Ralph, J.; Boerjan, W. lignin biosynthesis and structure. Plant Physiol. 2010, 153, 895–905.
(7) Anderson, E. M.; Stone, M. L.; Katahira, B.; Reed, M.; Muchero, W.; Ramirez, K. J.; Beckham, G. T.; Román-Leshkov, Y. Differences in S/G ratio in natural poplar variants do not predict catalytic depolymerization monomer yields. Nat. Commun. 2019, 10, 2033.
(8) Vardanyan, R. S.; Hruby, V. J. Synthesis of Best-Seller Drugs; Academic Press: Amsterdam, 2016.
(9) Sun, Z.; Frölich, B.; De Santi, A.; Elangovan, S.; Barta, K. Bright side of lignin depolymerization: Toward new platform chemicals. Chem. Rev. 2018, 118, 614–678.
(10) Schützner, W.; Rinders, T.; van den Bosch, S.; Koelewijn, S.-F.; Beckham, G. T.; Sels, B. F. Chemicals from lignin: an interplay of lignocellulosic fractionation, depolymerisation, and upgrading. Chem. Soc. Rev. 2018, 47, 852–908.
(11) Galkin, M. V.; Samec, J. S. M. Lignin valorization through catalytic lignocellulosic fractionation: a fundamental platform for the future bioeconomy. ChemSusChem 2016, 9, 1544–1558.
(12) Shuai, L.; Amiri, M. T.; Questell-Santiago, Y. M.; Héroguel, F.; Li, Y.; Kim, H.; Meilan, R.; Chapple, C.; Ralph, J.; Luterbacher, J. S. Formaldehyde stabilization facilitates lignin monomer production during biomass depolymerization. Science 2016, 354, 329–333.
(13) Lan, W.; Amiri, M. T.; Hunston, C. M.; Luterbacher, J. S. Protection group effects during α,γ-diol lignin stabilization promote high-selectivity monomer production. Angew. Chem., Int. Ed. 2018, 57, 1356–1360.
(14) Rahimi, A.; Ulbrich, A.; Coon, J. J.; Stahl, S. S. Formic-acid-induced depolymerization of oxidized lignin to aromatics. Nature 2014, 515, 249–252.
(15) Tuck, C. O.; Pérez, E.; Horváth, I. T.; Sheldon, R. A.; Poliaikoff, M. Valorization of biomass: deriving more value from waste. Science 2012, 337, 695–699.
(16) Upton, B. M.; Kasko, A. M. Strategies for the conversion of lignin to high-value polymeric materials: review and perspective. Chem. Rev. 2016, 116, 2275–2306.
(17) Zhao, S.; Abu-Omar, M. M. Renewable thermoplastics based on lignin-derived polyphenols. Macromolecules 2017, 50, 3573–3581.
(18) Blonda, E.; Bonom, J.; Smolker, M.; Kaval, N.; Lémière, F.; Sergeyev, S.; Diels, L.; Sels, B.; Mæs, B. U. W. Bio-based aromatic amines from lignin-derived monomers. ACS Sustainable Chem. Eng. 2019, 7, 6906–6916.
(18) Robinson, A. M.; Hensley, J. E.; Medlin, J. W. Bifunctional catalysts for upgrading of biomass-derived oxygenates: a review. ACS Catal. 2016, 6, 5026–5043.
(19) Kasparek, S. 1-, 2-, and 3-Benzazepines. Adv. Heterocycl. Chem. 1974, 17, 45–98.
(20) Marcus, Y. Deep Eutectic Solvents; Springer Nature: Switzerland, 2018.
(21) Jérôme, F.; Luque, R. Bio-Based Solvents; John Wiley & Sons Ltd: Hoboken, 2017; Ch. 3.
(22) Abbott, A. P.; Boothby, D.; Capper, G.; Davies, D. L.; Rasheed, R. K. Deep eutectic solvents formed between choline chloride and carboxylic acids: versatile alternatives to ionic liquids. J. Am. Chem. Soc. 2004, 126, 9142–9147.
(23) Bühn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. The catalytic amination of alcohols. ChemCatChem 2011, 3, 1853–1864.
(24) Irriog, T.; Kempe, R. 3d-Metal catalyzed N- and C-alkylation reactions via borrowing hydrogen or hydrogen auto-transfer. Chem. Rev. 2019, 119, 2524–2549.
(25) Yan, T.; Feringa, B. L.; Barta, K. Direct N-alkylation of unprotected amino acids with alcohols. Sci. Adv. 2017, 3, eaa06494.
(26) Vittorino, E.; Sortino, S. A phenolic antioxidant releasing nitric oxide on demand. Eur. J. Org. Chem. 2010, 2010, 421–426.
(27) Snow, A. D.; Nguyen, B. P.; Castillo, G. M.; Sanders, V. J.; Lake, T. P.; Larsen, L.; Weavers, R. T.; Lorimer, S. D.; Larsen, D. S.; Cofen, D. L. D. Compounds, compositions and methods for the treatment of amyloid diseases and synucleinopathies such as Alzheimer’s disease, type 2 diabetes, and Parkinson disease, U.S. patent WO03/101927A1, 2003.
(28) Curia, S.; Biundo, A.; Fischer, I.; Braunschmid, V.; Göbitz, G. M.; Stanzione, J. F. Towards sustainable high-performance thermoplastics: synthesis, characterization, and enzymatic hydrolysis of bisguaiacol-based polyesters. ChemSusChem 2018, 11, 2529–2539.
(29) Shen, Y.; Sheng, R.; Zhang, J.; He, Q.; Yang, B.; Hu, Y. 2-Phenoxy-indan-1-one derivatives as acetylcholinesterase inhibitors: a study on the importance of modifications at the side chain on the activity. Bioorg. Med. Chem. 2008, 16, 7746–7753.
(30) Klein, C. D. P.; Klingmüller, M.; Schellinski, C.; Landmann, S.; Hauschild, S.; Heber, D.; Mohr, K.; Hopfinger, A. J. Synthesis, pharmacological and biophysical characterization, and membrane-interaction QSAR analysis of cationic amphiphilic model compounds. J. Med. Chem. 1999, 42, 3874–3888.
(31) Calcaterra, N. E.; Barrow, J. C. Classics in chemical neuroscience: diazepam (valium). ACS Chem. Neurosci. 2014, 5, 253–260.
(32) Shah, J. H.; Hindupur, R. M.; Pati, H. N. Pharmacological and biological activities of benzazepines: an overview. Curr. Bioact. Compd. 2015, 11, 170–188.
(33) Feuston, B. P.; Culverson, J. C.; Duggan, M. E.; Hartman, G. D.; Leu, C. T.; Rodan, S. B. Binding model for nonpeptide antagonists of α7 n integrin. J. Med. Chem. 2002, 45, 5640–5648.
(34) Mach, U. R.; Hackling, A. E.; Perachon, S.; Ferry, S.; Wermuth, C. G.; Schwartz, J. C.; Sokoloff, P.; Stark, H. Development of novel 1,2,3,4-tetrahydroisoquinoline derivatives and closely related compounds as potent and selective dopamine D1 receptor ligands. ChemBioChem 2004, 5, 508–518.
(36) Bradshaw, B.; Evans, P.; Fletcher, J.; Lee, A. T. L.; Mwashimba, P. G.; Oehlerich, D.; Thomas, E. J.; Davies, R. H.; Allen, B. C. P.; Broadley, K. J.; Hamrouni, A.; Escargueil, C. Synthesis of 5-hydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-ones: selective antagonists of muscarinic (M3) receptors. Org. Biomol. Chem. 2008, 6, 2138–2157.

(37) Jin, J.; Weinreb, S. M. Enantioselective total syntheses of the 5,11-methanomorphanthridine Amaryllidaceae alkaloids (−)-pancracine and (−)-coccinine. J. Am. Chem. Soc. 1997, 119, 2050–2051.

(38) Guillou, C.; Beunard, J.-L.; Gras, E.; Thal, C. An efficient total synthesis of (±) galanthamine. Angew. Chem., Int. Ed. 2001, 40, 4745–4746.

(39) Stein, M.; Breit, A.; Fehrentz, T.; Gudermann, T.; Trauner, D. Optical control of TRPV1 channels. Angew. Chem., Int. Ed. 2013, 52, 9845–9848.

(40) Kouznetsov, V.; Palma, A.; Ewert, C. Synthesis and applicability of partially reduced 2-benzazepines. Curr. Org. Chem. 2001, 5, 519–551.

(41) Katritzky, A. R.; Maimait, R.; Xu, Y.-J.; Akhmedova, R. G. A new synthesis of 2-benzazepines. Synthesis 2002, 2002, 601–604.

(42) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. The Pictet-Spengler reaction in nature and in organic chemistry. Angew. Chem., Int. Ed. 2011, 50, 8538–8564.

(43) Orazi, O. O.; Corral, R. A.; Giaccio, H. Synthesis of fused heterocycles: 1,2,3,4-tetrahydroisoquinolines and ring homologues via sulphonamidomethylation. J. Chem. Soc., Perkin Trans. 1 1986, 1977–1982.

(44) Yokoyama, A.; Obwada, T.; Shudo, K. Prototype Pictet-Spengler reactions catalyzed by superacids. involvement of dicationic superelectrophiles. J. Org. Chem. 1999, 64, 611–617.

(45) Ruß, C.; König, B. Low melting mixtures in organic synthesis - an alternative to ionic liquids? Green Chem. 2012, 14, 2969–2982.

(46) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Guillena, G.; Pastor, I. M.; Ramón, D. J. Deep eutectic solvents: the organic reaction medium of the century. Eur. J. Org. Chem. 2016, 2016, 612–632.

(47) Handy, S.; Wright, M. An acid-free Pictet–Spengler reaction using deep eutectic solvents (DES). Tetrahedron Lett. 2014, 55, 3440–3442.

(48) Ragauskas, A. J.; Beckham, G. T.; Biddy, M. J.; Chandra, R.; Chen, F.; Davis, M. F.; Davison, B. H.; Dixon, R. A.; Gilna, P.; Keller, M.; Langan, P.; Naskar, A. K.; Saddler, J. N.; Tschaplinski, T. J.; Tuskan, G. A.; Wyman, C. E. Lignin valorization: improving lignin processing in the biorefinery. Science 2014, 344, 1246843.

(49) Hornykiewicz, O. L-DOPA: from a biologically inactive amino acid to a successful therapeutic agent. Amino Acids 2002, 23, 65–70.

(50) Kilgore, M. B.; Kutchan, T. M. The Amaryllidaceae alkaloids: biosynthesis and methods for enzyme discovery. Phytochem. Rev. 2016, 15, 317–337.