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Glycerol Upgrading via Hydrogen Borrowing: Direct Ruthenium-Catalyzed Amination of the Glycerol Derivative Solketal

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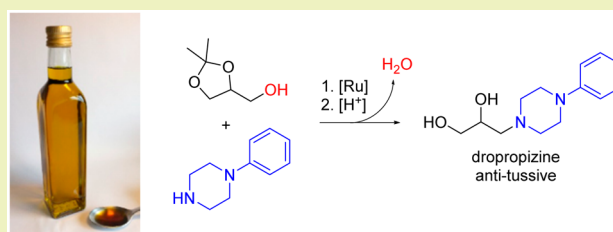
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S Supporting Information

ABSTRACT: Hydrogen borrowing provides an efficient and atom economical method for carbon–nitrogen and carbon–carbon bond formation from alcohol precursors. Glycerol is a renewable nontoxic polyol and a potential precursor to small functional organic molecules. We here report the direct amination of solketal, a 1,2-hydroxy-protected derivative of glycerol, via ruthenium-catalyzed hydrogen borrowing, affording up to 99% conversion and 92% isolated yield using $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ as the catalyst precursor. The synthesis of an antitussive agent in 86% overall yield from solketal was also demonstrated using this methodology.

KEYWORDS: Glycerol, Catalysis, Hydrogen borrowing, Ruthenium, Alcohol, Amine



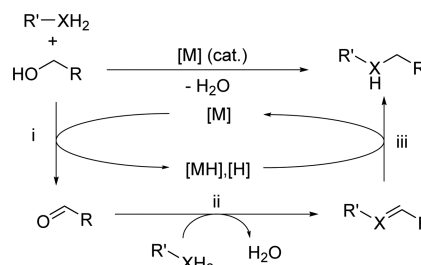
INTRODUCTION

Glycerol (1,2,3-propanetriol) is formed as a byproduct during hydrolysis or transesterification of vegetable oils. Due to the recent focus on biofuels, there is currently a world surplus of glycerol, which in turn has sparked an interest in finding new applications for this versatile raw material.¹ Precursors used for organic synthesis today mainly derive from petrochemical sources, and replacements originating from biomass need to be found. Glycerol is one of several platform chemicals under investigation in this context. Various processes have been developed for the transformation of glycerol into other useful molecules,^{2–4} involving selective oxidations,⁵ ester- and etherifications,^{6–8} as well as conversion to 1,2- or 1,3-propanediol,^{9–11} acrolein,¹² and glycerol carbonate.¹³ Glycerol can also be used as a solvent in organic reactions,¹⁴ and as a monomer for polymer synthesis.¹⁵ However, the scope of reactions for glycerol upgrading is still rather limited, and further research in this area is essential.

Hydrogen borrowing, also called borrowing hydrogen or hydrogen autotransfer, is a process that allows the direct coupling of alcohol functionalities with nucleophiles to form a new carbon–heteroatom or carbon–carbon bond.^{16–22} The reaction is generally catalyzed by a homogeneous transition metal complex based on ruthenium^{23–28} or iridium,^{29–36} although examples of iron-based catalysts have recently also been reported,^{37–44} further increasing the appeal of this reaction as a sustainable alternative to traditional approaches. Heterogeneous catalysts are also well-known to effect this type of transformation.⁴⁵

The catalytic cycle involves dehydrogenation of the alcohol to form a carbonyl group (Scheme 1, step i), nucleophilic attack

Scheme 1. Hydrogen Borrowing Reaction (M = Ru, Ir, or Fe; X = N or C)



on the carbonyl functionality (step ii), and final hydrogenation of the unsaturated intermediate (step iii) to form the desired compound.^{46,47} The nucleophiles are either nitrogen-based, i.e., amines, anilines, or sulfonamides, or carbon nucleophiles such as enolates or ylides. In most cases, water is the only byproduct, further adding to the “green” aspect of the reaction.

There are currently few examples of glycerol derivatives as substrates in the hydrogen borrowing reaction. In 2009, Williams and co-workers showed that isopropylideneglycerol

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(solketal) can be aminated with dimethylamine in 70% yield using a ruthenium catalyst.⁴⁸ Rueping and co-workers have demonstrated that the same protected glycerol substrate can undergo direct carbon–carbon bond forming reactions with enolates derived from acetophenone.⁴⁹ Inspired by earlier reports from the Madsen group,⁵⁰ Crotti and co-workers have shown that glycerol itself can react with diamines to form piperazine derivatives and benzimidazoles.⁵¹ An elegant one-pot conversion of glycerol to secondary amines via a combined microbial fermentation/hydrogen borrowing process was described by Marr.⁵² A few studies of other biomass-derived alcohols have been reported, but examples are as yet scarce.^{53,54}

We are interested in the derivatization of glycerol via hydrogen borrowing with the purpose of building small functional organic molecules that can be used further in organic transformations or employed directly in pharmaceutical applications. Potential drug targets where amination of glycerol units could play an important part are shown in Figure 1. We herein report our results from the direct coupling of the primary alcohol functionality of isopropylidenglycerol (solketal) with a variety of different amines.

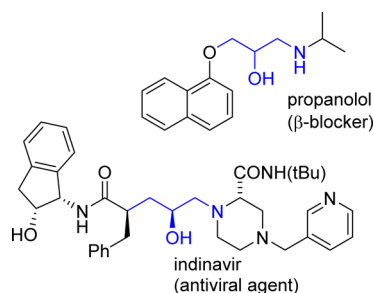


Figure 1. Potential applications for the catalytic amination of glycerol scaffolds.

RESULTS AND DISCUSSION

An initial investigation of ruthenium and iridium catalysts was first performed, using morpholine as the model amine in a hydrogen borrowing reaction with solketal. Reactions were performed in sealed vessels, allowing heating above the boiling point of the solvent, using equimolar amounts of the two

starting materials. The conversion was measured by ¹H NMR analysis of the crude product. Results from these initial experiments are displayed in Table 1.

Several catalysts that have proven efficient in the amination of primary alcohols were explored. [Ru₃(CO)₁₂], previously used by Beller⁵⁵ and Vogt²⁶ in the amination of alcohols with ammonia, was unsuccessful in this case, affording only unreacted starting material (entry 1). [Cp*IrCl₂]₂³⁰ was more successful, affording the desired amine **2**, albeit in a moderate yield. (entry 2). Williams and co-workers have shown that [Ru(*p*-cymene)Cl₂]₂ is an efficient catalyst for the amination of both primary and secondary alcohols.⁴⁸ Initial attempts using this catalyst gave a low conversion when the reaction was performed at 110 °C with dppe as the ligand (entry 3). As several of these catalytic systems have been applied at higher temperatures, the reaction temperature was raised to 130 °C, and after a reaction time of 48 h, complete conversion of the alcohol to the aminated product was achieved (entry 4). Shorter reaction times, as well as lowering the reaction temperature to 120 °C, gave a slight decrease in conversion (entries 5–7).

Under optimized conditions, only starting materials and product could be seen by ¹H NMR. In the presence of an internal standard (1,4-di-*tert*-butylbenzene), a total material balance in the range 91–94% was found. At lower conversions, trace amounts of the intermediate aldehyde and imine could be detected by ¹H NMR, but these compounds are not seen in the crude product after the full reaction time.

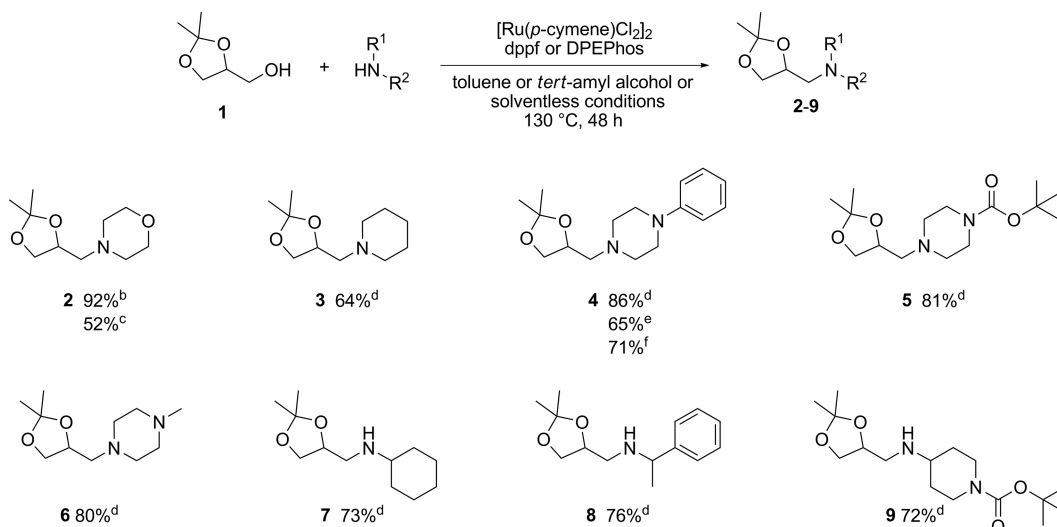
A reaction employing DPEphos as the ligand was also performed (entry 8), affording nearly the same outcome as the corresponding reaction with dppe (entry 5). For further experiments, [Ru(*p*-cymene)Cl₂]₂ with either dppe or DPEphos as ligand was thus employed, and reactions were performed in toluene at 130 °C for 48 h.

With the optimized reaction conditions at hand, a selection of amines were then examined in the direct amination reaction (Scheme 2), employing a slight excess of amine to solketal. Under optimized conditions, the morpholine derivative **2** was isolated in 92% yield. Piperidine as the amine gave the desired product **3** in a 64% yield, with the moderate yield in this case mainly a result of purification difficulties for this specific product. Substituted piperazines such as 1-phenylpiperazine, 1-Boc-piperazine, and 1-methylpiperazine were also applicable,

Table 1. Screening of Reaction Conditions for the Amination of Solketal (**1**) with Morpholine^a

entry	catalyst	cat. amount [mol %]	temp [°C]	time [h]	NMR yield ^b [%]
1 ^c	[Ru ₃ (CO) ₁₂]	2	140	24	<1
2 ^{c,d}	[Cp*IrCl ₂] ₂	5	110	24	38
3	[Ru(<i>p</i> -cymene)Cl ₂] ₂	1.25	110	24	12
4	[Ru(<i>p</i> -cymene)Cl ₂] ₂	1.25	130	48	>99
5	[Ru(<i>p</i> -cymene)Cl ₂] ₂	1.25	130	24	95
6	[Ru(<i>p</i> -cymene)Cl ₂] ₂	1.25	130	12	90
7	[Ru(<i>p</i> -cymene)Cl ₂] ₂	1.25	120	24	80
8 ^e	[Ru(<i>p</i> -cymene)Cl ₂] ₂	1.25	130	24	97

^aConditions: catalyst, dppe (0.05 mmol for entries 3–7), morpholine (2 mmol), solketal (2 mmol), and toluene (2 mL) were stirred at room temperature for 5–10 min, then heated for 24 h under an atmosphere of argon. ^bMeasured by ¹H NMR. ^cNo dppe added. ^dIn 0.1 mL toluene using 5 mol % NaHCO₃ as added base. ^eDPEphos as ligand. Reaction performed on 1 mmol scale.

Scheme 2. Amination of Solketal^a

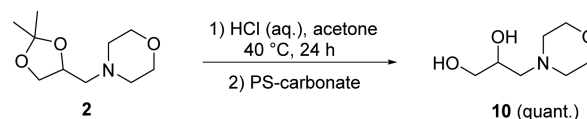
^aConditions: [Ru(*p*-cymene)Cl₂]₂ (0.025 mmol), ligand (0.05 mmol), amine (2.4 mmol), solketal (2 mmol), and toluene (2 mL) were stirred at room temperature for 5–10 min, then heated at 130 °C for 48 h under an atmosphere of argon. ^bdppf as the ligand. ^c*tert*-Amyl alcohol as solvent. ^dDPEPhos as ligand. ^eSolventless conditions, ratio amine/solketal 1/1.5. ^fSolventless conditions, ratio amine/solketal 1.2/1.

and amination products 4, 5, and 6 were isolated in 86%, 81%, and 80%, respectively. Coupling with these types of substrates would be important for target molecules such as indinavir (Figure 1). Sterically demanding primary amines were also successful. Cyclohexylamine derivative 7 was produced in 73% yield, while α -methylbenzylamine as the amine component afforded 76% of product 8. 4-Aminopiperidine is an important building block for drugs such as the pain reliever fentanyl.⁵⁶ With the use of 4-amino-*N*-Boc-piperidine as the amine, compound 9 could be isolated in 72% yield, providing a highly functionalized scaffold for further derivatization after deprotection. Although bulkier primary amines performed well, less hindered primary amines such as *n*-hexylamine, 2-phenethylamine, and *N,N'*-dimethylpropane-1,3-diamine afforded a low conversion (products not isolated). Benzylamine somewhat surprisingly also gave a low conversion, while its α -methylated counterpart (see 8 in Scheme 2) afforded a satisfactory result. MS analysis of reactions involving *n*-hexylamine or benzylamine indicated some dimerization of the primary amine, a known reaction that is more commonly associated with the more active iridium catalysts,⁵⁷ and this may be an explanation for the low conversions when these amines are employed.

To investigate if a more sustainable solvent than toluene could be employed, the reaction in Table 1 was also performed in *tert*-amyl alcohol, using the conditions shown in Scheme 2, with DPEPhos as the ligand. Product 2 could be isolated in this case also, albeit in a lower yield (52%) than for toluene, suggesting that although alcoholic solvents are applicable, further optimization of the reaction conditions are needed to augment the product yield. However, the use of solventless conditions was more promising. While an excess of solketal to amine afforded 65% of compound 4 after isolation, the same reaction using instead a slight excess of amine afforded a respectable yield of 71%, indicating that these amination reactions can be performed under greener conditions with a satisfactory outcome.

Deprotection of the morpholine derivative 2 was also investigated (Scheme 3). Several conventional methods for the deprotection of acetonides (HOAc, TFA, *p*-TsOH, HCl in

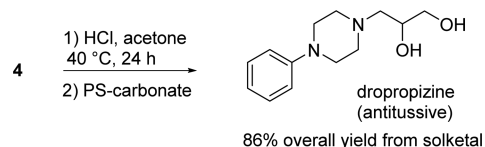
Scheme 3. Acetal Deprotection Affording Glycerol Aminated at the Terminal Carbon



acetone, Dowex-50W-8X ion-exchange resin) were examined for removal of the acetal protecting group. Stirring the protected amino diol in aqueous HCl in acetone at 40 °C for 24 h gave the best results, affording the hydrochloride salt of the free amino diol, which was subsequently neutralized using a polymer-bound carbonate base, allowing facile purification via filtration to afford aminodiols 10 in quantitative yield.

Dropropazine is an antitussive agent included in a number of commercial cough suppressants. Deprotection of the ketal functionality in 4 using the conditions described above allowed the isolation of dropropazine in quantitative yield from 4 and 86% overall yield from solketal (Scheme 4).

Scheme 4. Synthesis of a Cough Suppressant

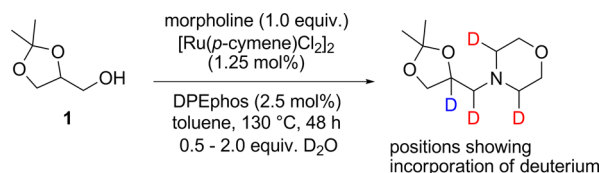


To investigate if the addition of D₂O to the system would result in the incorporation of deuterium into the product, the reaction between solketal and morpholine was repeated with varying amounts of added D₂O.^{58,59} There are only a limited number of mechanisms that can exchange the proton/hydrogen character of hydrogens in hydrogen transfer reactions. In metal-free or Lewis-acid-catalyzed hydride transfer reactions, such as Meerwein–Ponndorf–Verley or Cannizzaro, the proton is removed by a base, and the α -oxo hydride is directly transferred to a carbonyl. In this type of mechanism, or in the substrates, there are no opportunities for scrambling of the proton and the

hydride. In the presence of a metal, there are two major mechanistic possibilities, the mono- and dihydride routes. In the dihydride route, both proton and hydride are transferred to the same metal center, formally giving rise to a metal dihydride. In this scenario, the proton and hydride lose their identities, and full scrambling is expected. In a deuterium-enriched protic solvent, where the proton has had time to equilibrate, we thus expect significant deuterium incorporation at the α -position. For the monohydride route, we expect only α -hydrides to migrate to the metal; the proton can be lost to a base, or migrate to a basic ligand position. In general, no scrambling is expected in such cases. The exception would be if the metal hydride is both long-lived and redox-labile, in which case the “hydride” could be delivered as a proton to the medium, reducing the metal reversibly.⁶⁰ In such a scenario, scrambling between acidic “hydrides” on metal and deuterium in a protic solvent would be expected.⁴⁷

For the deuterium exchange reactions, the conditions shown in Scheme 2 were employed, but with the addition of 0.5, 1.0, and 2.0 equiv of D₂O relative to solketal and using a 1:1 ratio of solketal to amine to facilitate analysis. For all three reactions, ¹H NMR indicated the incorporation of deuterium mainly at the positions shown in Scheme 5 (see Supporting Information),

Scheme 5. Deuterium Incorporation upon Addition of D₂O to the Reaction Mixture



i.e. on the three carbon atoms bonded to nitrogen (marked in red in Scheme 5), as well as at the CH position (marked in blue). The extent of deuterium incorporation increases with the amount of D₂O added, and was analyzed by a combination of disappearance in ¹H NMR, appearance in ²H NMR, and presence of typical triplets in ¹³C NMR. Major incorporations (overlapping in H NMR, but similar in all three positions according to ¹³C NMR) were seen at the positions marked in red in Scheme 5, while the blue deuterium indicates lower incorporation level. Other positions α to heteroatoms also showed minor incorporation of D.

A plausible mechanism for deuterium incorporation is shown in Scheme 6. The high level of D-incorporation in the morpholine moiety indicates that the initially formed

immonium intermediate is in rapid equilibrium with an immonium ion in the ring. This is formally a 1,3-hydride shift, but is most probably catalyzed by the ruthenium complex. The final product could be formed by addition of a ruthenium deuteride to these intermediates, clearly showing that the initially formed ruthenium hydride has lost a proton to solvent in a fast, reversible reaction. The lower levels of incorporation at other positions can be explained by reversible loss of protons from the immonium intermediate, giving rise to enamines, and by Ru-catalyzed alkene isomerization.

A chiral ligand was also investigated in the reaction system. Reactions with morpholine and 1-phenylpiperazine were repeated using (S)-BINAP as the ligand, affording an enantiomeric excess of 5% for product 2, and 18% ee for compound 4. Although these enantioselectivities are not synthetically useful, they provide conclusive evidence that the phosphine is involved in the selectivity-determining step.

CONCLUSIONS

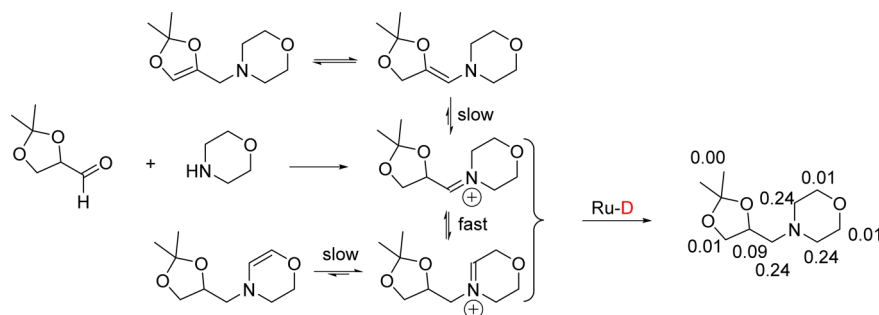
We have shown that the protected glycerol derivative solketal (isopropylidenglycerol) can be aminated with secondary and sterically demanding primary amines in the primary position employing [Ru(*p*-cymene)Cl₂]₂ as the precatalyst, using either toluene or *tert*-amyl alcohol as the solvent, or performing the reaction under solventless conditions. Solketal reacted efficiently with secondary amines such as morpholine, piperidine, 1-phenylpiperazine, and 1-Boc-piperazine, forming the desired coupling products in up to 92% isolated yield. Moreover, hindered primary amines (α -methylbenzylamine, cyclohexylamine) were also suitable substrates, affording aminated products in 70–73% yield, while less hindered primary amines were inefficient in this reaction. Deprotection under acidic conditions, followed by neutralization with a polymer-bound base, afforded the free aminated diol. We envisage that the developed methodology can contribute toward the replacement of current fossil-derived organic precursors with more sustainable alternatives.

EXPERIMENTAL SECTION

Materials. Chemicals were purchased from commercial sources and used as received. Solvents were purchased as anhydrous grade with the exception of *tert*-amyl alcohol which was purchased as ReagentPlus grade. MP-carbonate (MP = macroporous polystyrene, capacity 3.18 mmol/g) was purchased from Argonaut Technologies (now Biotage). All reactions were run under an argon atmosphere unless otherwise stated.

¹H, ²H, and ¹³C NMR spectra were acquired on a Varian MR 400 MHz instrument or on a Varian VNMR-S 500 MHz. ¹H, ²H, and ¹³C

Scheme 6. Plausible Mechanistic Pathways for Deuterium Incorporation, and Approximate Level of Incorporation As Determined by ¹H, ²H, and ¹³C NMR



NMR were performed in CDCl₃, CD₃OD, or toluene-*d*₈ using residual solvent peaks for reference. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad.

Compounds **2**, **4**, **10**, and dropropizine have been reported earlier, and for **2** and **10** only ¹H and ¹³C NMR data are provided here. For compound **4**, the original reference does not include full characterization of the compound, and this data is thus included in the Supporting Information.

FTIR was performed on a PerkinElmer Frontier FTIR Spectrometer with or without an ATR device using Spectrum software. HRMS was performed on a Waters Xevo QTOF (ionization mode ESI+): column, Acquity UPLC CSH C8 column (100 mm × 2.1 mm, 1.7 μm particles); gradient, 5–95% acetonitrile in 1 mM ammonium formate/10 mM formic acid at pH 3; flow rate, 0.7 mL/min; temp, 60 °C.

General Procedure for the Amination of DL-Isopropylidene-glycerol. [Ru(*p*-cymene)Cl₂]₂ (15 mg, 0.025 mmol, 1.25 mol %) and dppe or DPEPhos (0.05 mmol, 2.5 mol %) were added to a Biotage 2–5 mL MW-vial. The reaction vessel was sealed and purged with argon. Amine (2.4 mmol, 120 mol %) and DL-isopropylidene-glycerol (250 μL, 2 mmol, 100 mol %) were added, followed by the dropwise addition of toluene (2 mL) or *tert*-butanol (2 mL), or the reaction was run under solventless conditions. When using solventless conditions, an amine/solketal ratio of either 1.2/1 (as for the other experiments) or 1/1.5 was employed. The mixture was stirred at room temperature for 5 min and then heated at 130 °C (oil bath temperature) for 48 h. The mixture was cooled to room temperature; the solvent was removed under reduced pressure to give a crude product, and the conversion was measured. The crude mixture was subsequently diluted with dichloromethane and washed with water, or diluted with ethyl acetate and washed with brine. The extraction is performed to remove unreacted solketal and is only necessary if a low conversion is obtained according to ¹H NMR analysis of the crude product. The solvent was removed under reduced pressure, and the remaining crude product was purified using flash column chromatography on silica gel (eluent: 0–30% MeOH in dichloromethane or 0–45% EtOAc in petroleum ether). Reactions were performed on a scale varying from 1 to 4 mmol.

Deprotection of **2 To Afford 3-Morpholino-1,2-propanediol (**10**).**⁶¹ 4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)morpholine (**2**, 100 mg, 0.497 mmol) was dissolved in a mixture of 0.1 M HCl:acetone 1:1 (20 mL) and stirred at 40 °C for 24 h. The mixture was then evaporated to dryness to give a dark yellow oil. ¹H and ¹³C NMR of the crude product indicated the formation of 3-morpholino-1,2-propanediol hydrochloride (**10**·HCl) of high purity (see page S16 for NMR spectra, Supporting Information). The crude **10**·HCl (80.1 mg, 0.497 mmol) was dissolved in methanol (6 mL), and MP-carbonate (156 mg, 0.497 mmol) was added. The mixture was stirred at room temperature for 48 h and then filtered to remove the MP-carbonate. The solvent was removed under reduced pressure to afford **10** (245 mg, 98%) as a brown oil. δ_{H} (400 MHz, CD₃OD): 2.45–2.71 (6H, m, NCH₂CH₂ and NCH₂CH), 3.47–3.57 (2H, m, CH₂OH), 3.69–3.75 (4H, t, CH₂OH), 3.80–3.87 (1H, m, CHOH); δ_{C} (100 MHz, CD₃OD) 55.2, 62.8, 66.1, 67.5, 69.4.

Deprotection of **4 To Afford 3-(4-Phenylpiperazin-1-yl)-propane-1,2-diol (Dropropizine).** This results in quantitative, unpurified, brown solid. δ_{H} (400 MHz, CDCl₃): 2.42 (1H, dd, *J* = 3.9 and 12.5 Hz, NCH₂CHOH), 2.58–2.67 (3H, m, PhNCH₂CH₂N and NCH₂CHOH), 2.80–2.85 (2H, m, PhNCH₂CH₂N), 3.16–3.25 (4H, m, PhNCH₂CH₂N), 3.53 (1H, dd, *J* = 4.4 and 11.4 Hz, CH₂OH), 3.75–3.79 (1H, m, CH₂OH), 3.84–3.90 (1H, m, CHOH), 6.85–6.89 (1H, m, Ph), 6.91–6.94 (2H, m, Ph), 7.24–7.29 (2H, m, Ph); δ_{C} (100 MHz, CDCl₃) 49.2, 53.5, 60.4, 65.0, 67.0, 116.3, 120.0, 129.3, 151.3.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.6b01659.

Characterization data for compounds **2–9**; experimental details for the deuterium incorporation studies; and ¹H, ²H, and ¹³C NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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