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Combined Photoredox and Lewis Acid Catalyzed α-Hydroxyalkylation of Cyclic Ethers with Aromatic Ketones

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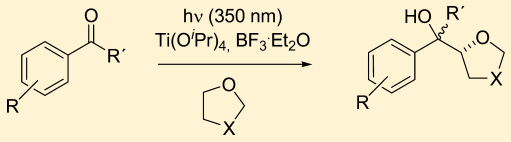
Supporting Information

ABSTRACT: The photochemically induced coupling of aromatic ketones with cyclic ethers such as tetrahydrofuran, tetrahydropyran, and 1,4-dioxane was studied. Direct photolysis of the substrates with UV-A light centered at 350 nm does not lead to photoinduced hydrogen transfer whereas the addition of a mixture of the Lewis acid catalysts $Ti(O^iPr)_4$ and BF_3 enables the formation of the hydroxyalkylation products.



INTRODUCTION

Carbon−carbon bond forming processes using photoredox catalysis are currently complementing the well-established repertoire of transition metal catalysis and organocatalytic methods.[1] Photoredox catalysis adds one remarkable aspect, the large energy excess deposited in the electronically excited catalyst able to trigger oxidative or reductive quenching processes that are energetically highly improbable from the corresponding electronic ground states.[2] This allows also processes that are endergonic in total to be accomplished due to the high additional energy input by initial photoexcitation.[3] These processes can open the pathway to new reactivities and selectivities and also new product types useful for organic synthesis.[4]

When looking for new applications of photoredox-initiated reactions, one might consider three classes of chemical reactions: (i) thermal processes known from metal- or organocatalysis that are adopted and modified by photocatalysis (e.g., α-alkylation of enamines), (ii) photochemical processes that are modified and improved by photocatalysis (e.g., [2 + 2]-photocycloadditions), or (iii) new processes that were not yet realized by thermal or photochemical processes. Route iii is most demanding but obviously highly desirable. Photoinduced reactions that deserve special attention, beside the impressive playground of cycloaddition chemistry, are hydrogen transfer processes from otherwise hard-to-activate CH positions.[5] Photoexcited substrates that are able to abstract hydrogen atoms are triplet states of aromatic carbonyl compounds because of their long lifetimes and high excitation energies.[6] Two distinct modes for hydrogen transfer are possible: hydrogen atom transfer or proton-involved hydrogen transfer processes. The second route might involve a deprotonation/electron transfer sequence or an oxidation step followed by proton transfer.[7] For applications in photoredox catalysis, the last sequence is the most relevant because of the oxidative capability of many photoexcited catalysts, such organic dyes,[8] transition metal complexes,[9] or semiconductor particles.[10]

RESULTS AND DISCUSSION

We have recently reported on modifications of the Ti(IV)-mediated photochemical hydroxymethylation of ketones and keto esters.[11] The Lewis acid−base complex between the carbonyl acceptor and the titanium metal center (from $Ti(OR)_2Cl_2$) enables photoinduced electron transfer from the methanol in the ligand sphere to the carbonyl acceptor **1**. Subsequent proton transfer and radical−radical combination delivers the hydroxymethylation product **2**. In case of insufficient Lewis acidity of the titanium complex $Ti(OR)_4$, the addition of a second Lewis acid (e.g., BF_3 or $AlCl_3$) enables the return to initial activity. The titanium catalyst with the lowest redox activity, $Ti(O^iPr)_4$, still enables the formation of reduction products (i.e., 1-arylethanols) when applied without the second Lewis acid. A logical extension of this process is the C−C coupling of carbonyl components with α-ether radicals, a process already known from direct photolyses of carbonyl compounds in ethereal solvents such as tetrahydrofuran.[12,13] These direct excitations need short-wavelength irradiation (usually the 254 nm mercury line) and by nature turn on the unimolecular carbonyl photochemistry, as well as the typical reactions of electronically excited carbonyl compounds in the presence of hydrogen donors such as the prevailing pinacol formation. The α-ether alkyl radicals that are formed in these reactions can also undergo a series of addition reactions to electron-poor alkenes.[14,15] The processes that involve free ketyl radicals are often accompanied by the formation of the carbonyl pinacol coupling products and thus do not allow conversions with high yields and selectivities. Furthermore, direct excitation of carbonyl compounds does require short-wavelength irradiation (λ = 254−300 nm). Therefore, we envisaged to transfer our experience from our hydroxymethylation studies to the α-hydroxyalkylation of ethers (Scheme 1).

In order to optimize the reaction conditions for long wavelength excitation of ketone/ether solutions, we applied $TiCl_4$, nanosized titanium dioxide, $Ti(O^iPr)_4$, and $Ti(O^iPr)_4$/BF_3 as catalysts for the reaction of acetophenone (**1a**) with tetrahydrofuran (Scheme 2, Table 1). The highly Lewis acidic

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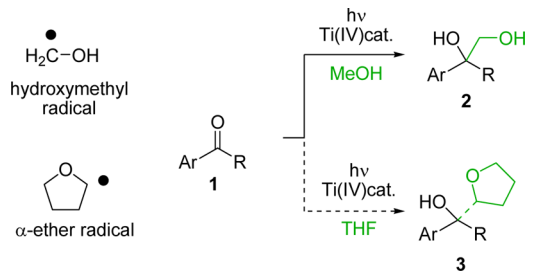
Scheme 1. Coupling Routes of C-Radical Formed by Photoinduced Electron Transfer with Aromatic Carbonyl



Scheme 2. Model Photoreaction of Acetophenone with Tetrahydrofuran

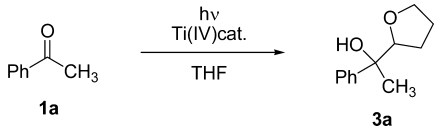


Table 1. Photolysis of Acetophenone in Tetrahydrofuran in the Presence of Titanium Reagents

entry[a]	catalyst	yield **3a** (%)	threo/erythro[f]
1	0.5 equiv of $TiCl_4$[b]		
2	2.5 mg of TiO_2 P25	50[c]	51:49
3	0.5 equiv of $Ti(O^iPr)_4$		
4	**0.5 equiv of $Ti(O^iPr)_4$/1 equiv of BF_3**	**94**,[d] **87**[e]	**54:46**
5	0.5 equiv of $Ti(O^iPr)_4$/0.5 equiv of BF_3	74[d]	54:46
6	0.25 equiv of $Ti(O^iPr)_4$/0.5 equiv of BF_3	72[d]	54:46
7	0.1 equiv of $Ti(O^iPr)_4$/0.2 equiv of BF_3	37[d]	53:47
8	no catalyst or irradiation		
9	0.5 equiv of $Ti(O^iPr)_4$/1 equiv of BF_3/no irradiation		

[a]Reaction conditions: 0.75 mmol of acetophenone (**1a**) in tetrahydrofuran (6 mL) was irradiated (λ = 350 nm) for 48 h at room temperature under argon in the presence of the catalyst. [b]λ = 300 nm. [c]Yield determined via NMR, acetophenone pinacol was formed as side product with 40%. [d]yield by GC. [e]isolated yield. [f]by H NMR, crude reaction mixture.

titanium tetrachloride is not able to induce bond formation even under 300 nm excitation. At the excitation wavelengths applied for the other experiments (λ = 350 ± 30 nm), no reactivity was observed in the absence of Lewis acids because of the very low absorptivity of acetophenone. A slurry of titanium dioxide particles (applied as a 7:3 anatase–rutile mixture) and even better a mixture of $Ti(O^iPr)_4$ and BF_3 led to high conversions and high yields of the coupling product **3a**.

The latter reaction is catalytic in both Lewis acids (entries 5–7). Under titanium dioxide catalysis, the pinacol from acetophenone was formed as an additional product in about 40%, a typical side-reaction for semiconductor photocatalysis that was also observed in the hydroxymethylation of acetophenone.[11] In a second set of experiments, the application of the optimized conditions to the reaction of benzophenone, benzaldehyde, and four methylated substrates was investigated (Scheme 3, Table 2). Benzophenone tends to the formation of the tetraphenylpinacol under reductive conditions, whereas benzaldehyde tends to the formation of benzylic alcohol. These products were also found under standard conditions beside moderate yields of the CC-coupling products to THF, **3b** and **3c**.

Scheme 3. Aromatic Ketones and Benzaldehyde Coupling with Tetrahydrofuran

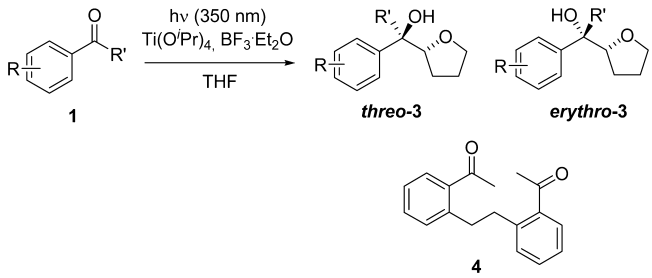


Table 2. Photolysis of Aromatic Ketones in Tetrahydrofuran in the Presence of $Ti(O^iPr)_4/BF_3$

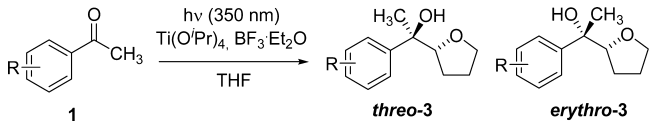
entry[a]	product	Ar	R′	yield[b] (%)	threo/erythro[e]
1	**3a**	Ph	CH_3	87	54:46
2	**3b**	Ph	C_6H_5	36[c]	
3	**3c**	Ph	H	19	48:52
4	**3d**	4-MeC_6H_4	CH_3	67	51:49
5	**3e**	3- MeC_6H_4	CH_3	66	49:51
6	**3f**	2-MeC_6H_4	CH_3	*d*	
7	**3g**	2,4,6-$(CH_3)_3C_6H_2$	CH_3		

[a]Reaction conditions: 1 equiv of ketone, 0.5 equiv of $Ti(O^iPr)_4$, and 1 equiv of BF_3·Et_2O in tetrahydrofuran was irradiated (λ = 350 nm) for 48 h at rt under argon. [b]Isolated yields. [c]No diastereoisomers are formed here. [d]Traces. [e]By ^1H NMR, crude reaction mixture.

The radical-induced benzaldehyde addition to THF is a well-studied reaction in borane-induced THF radical formation.[16] The methylated substrates **1d–1g** gave results that depend strongly on the ring position of the methyl substituents. From the meta- and para-methylated substrates, identical yields of products **3** were determined whereas the ortho substrate **1f** gave only traces (<5%) of **3f** and the mesityl derivative **1g** showed no product formation at all. From substrate **1f**, the coupling product **4**[17] was isolated in 25% yield, possibly deriving from the hydroxyl ortho-quinodimethane formed by intramolecular hydrogen transfer (in analogy to the photochemistry of 2-methylbenzophenone).[18] This observation is interesting because no direct excitation of the substrate **1f** is possible under these conditions, and thus, the formation of **4** has to be conducted via its radical anion.

In a third set of experiments, the application of the optimized conditions to a series of acetophenone derivatives was investigated (Scheme 4, Table 3). In the series of halogenated

Scheme 4. Photocatalytic Acetophenone Derivative Coupling with Tetrahydrofuran



acetophenone derivatives, the 4-fluoro and 4-chloro derivatives **1h** and **1k**, respectively, showed superior reactivity; the 2-fluoro and 2-methoxy derivatives **1i** and **1n** gave the alkylation products in moderate yields. Only low yields were obtained from 4-bromoacetophenone due to increasing reactivity at the aromatic nucleus (i.e., formation of substitution products at the phenyl

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Table 3. Photolysis of Acetophenone Derivatives in Tetrahydrofuran in the Presence of $Ti(O^iPr)_4/BF_3$

entry[a]	product	Ar	yield[b] (%)	threo/erythro[e]
1	**3h**	4-F-C_6H_4	82	52:48
2	**3i**	2-F-C_6H_4	42	59:41
3	**3j**	C_6F_5		
4	**3k**	4-Cl-C_6H_4	64	51:49
5[c]	**3l**	4-Br-C_6H_4	6[d]	
6	**3m**	4-MeO-C_6H_4		
7	**3n**	2-MeO-C_6H_4	22	57:43
8	**3o**	4-NO_2-C_6H_4		
9	**3p**	2-NO_2-C_6H_4		

[a]Reaction conditions: 1 equiv of ketone, 0.5 equiv of $Ti(O^iPr)_4$, and 1 equiv of $BF_3{\cdot}Et_2O$ in tetrahydrofuran was irradiated (λ = 350 nm) for 48 h at rt under argon. [b]Isolated yield. [c]1 equiv of $Ti(O^iPr)_4$ and 2 equiv of $BF_3{\cdot}Et_2O$. [d]Yield of *erythro*-**3l**. [e]By ^1H NMR, crude reaction mixture.

group). Neither the perfluorinated substrate **1j** nor the nitro derivatives **1o**,**p** showed the desired reactivity.

Finally, the extension of this process to other cyclic ethers was investigated (Scheme 5, Table 4). Under standard conditions,

Scheme 5. Acetophenone Coupling with Cyclic Ethers

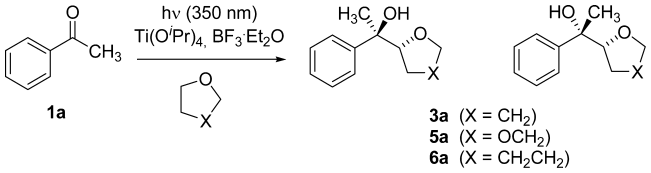

Table 4. Photolysis of Acetophenone and Cyclic Ethers in the Presence of $Ti(O^iPr)_4/BF_3$

entry[a]	ether	product	yield[b] (%)	threo/erythro[d]
1	tetrahydrofuran	**3a**	87	52:48
2	1,4-dioxane	**5a**	13[c]	*c*
3	tetrahydropyran	**6a**	25	55:45
4	1,3-dioxolane			

[a]Reaction conditions: 1 equiv of ketone, 0.5 equiv of $Ti(O^iPr)_4$, and 1 equiv of $BF_3{\cdot}Et_2O$ in tetrahydrofuran was irradiated (λ = 350 nm) for 48 h at rt under argon. [b]Isolated yield. [c]Only *erythro*-**5a** was isolated, and pinacol was formed as major product (26% yield). [d]By ^1H NMR, crude reaction mixture.

dihydropyran was reactive and coupling was a minor pathway beside pinacolization. Only the *erythro* diastereoisomer **5a** was isolated and characterized also by X-ray structure analysis. Better results were obtained with 1,4-dioxane where both diastereoisomers of **6a** were formed and could be separated and characterized by X-ray structure analyses (Figure 1). Unfortunately, 1,3-dioxolane, which is a formaldehyde equivalent, could not be applied because of rapid BF_3-induced polymerization.

CONCLUSION

The reaction of aromatic ketones in methanol solution in the presence of a Ti(IV) photoredox catalyst with low Lewis acidity ($Ti(O^iPr)_4$) leads to the formation of reduction products when performed by short-wavelength irradiation (λ = 300 nm).[11] The apparently low reactivity at excitation wavelengths >300 nm in the presence of this Ti(IV) photoredox catalysts can be attributed to the low absorbance of the redox-active species. The addition of a second Lewis acid leads to a switch in chemoselectivity and the formation of hydroxymethylation products but was also restricted to short-wavelength irradiation. In ethereal solutions, also long-wavelength irradiation leads to the formation of CC-coupling products, for example, **3a** from acetophenone (Scheme 6). This combination of Lewis-acid catalysis and photoactivation accounts for the mechanism as shown in Scheme 6. From the UV−vis spectra, of mixtures of acetophenone with one or two of the Lewis acids, no clear-cut decision about the absorbing species could be made because only an unstructured shoulder in the long-wavelength region appeared. The strong Lewis acid BF_3 (as THF complex in solution) forms a complex with the respective ketone and, in the presence of the Ti(IV) photoredox catalyst, is reduced to the radical species with concomitant formation of the ether radical cation. Subsequent proton transfer leads to a radical pair that combines to the coupling product **3a**.

EXPERIMENTAL PROCEDURES

General Aspects and Methods. All chemicals were purchased from commercial suppliers and were used as received. TiO_2 Aeroxide P25 was used. Tetrahydrofuran was dried by heating under reflux over sodium and then distilled. ^1H and ^{13}C NMR spectra were recorded at 300, 400, or 500 MHz for ^1H and 75.4, 100.5, or 125.7 MHz for ^{13}C. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonances of $CDCl_3$ as the internal standards (center line of the triplet at 77.0 ppm for ^{13}C and singlet at 7.26 ppm for ^1H). Gas chromatography equipped with a flame ionization detector (FID) was carried out with a HP-35 column as stationary phase and nitrogen as carrier gas. Gas chromatography coupled to mass spectrometry (GC-MS) measurements was carried out with a DB-5HT column as stationary phase and helium 5.0 (99.999% He) as carrier gas. For chemical ionization, methane was used. The exact ion mass measurements of compounds **3e**, **3h**, **3i**, **3k**, **3l**, and **3n** were conducted by EI-MS on a two sector instrument at a resolution of 3600 (10% valley definition) with appropriate internal standard ions from perfluorokerosene, PFK Uvasol (Merck, Darmstadt). Samples of compounds **3e**, **3h**, **3i**, **3k**, **3l**, and **3n** were introduced into the EI-MS ion source ($E_{kin}e^-$ = 70 eV; T = 473 K; $P = 10^{-6}$ bar) with a cooled direct inlet probe (273 K). The exact ion mass measurements were executed with an ICIS controlled peak matching algorithm. However, the very volatile analytes **3e**, **3h**, **3i**, **3k**, **3l**, and **3n** exhibit a disadvantageous vaporization behavior that lead to significant signal fluctuation of the

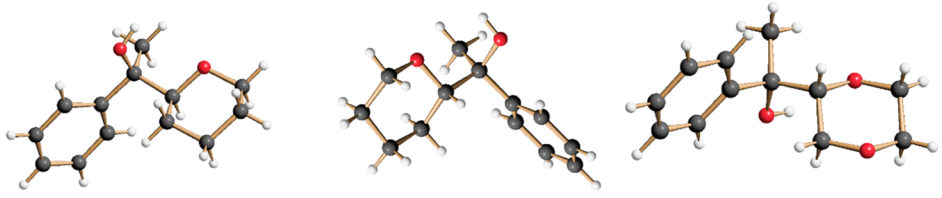

Figure 1. Structures of the acetophenone photoaddition products with tetrahydropyran (diastereoisomers *erythro*-**6a** and *threo*-**6a**) and with 1,4-dioxane (**5a**) in the crystal.

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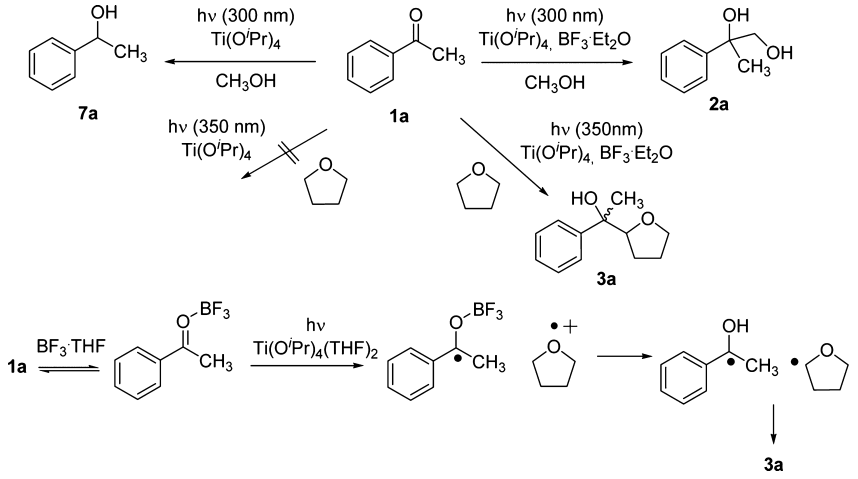
Scheme 6. Acetophenone Coupling Behavior Depending on Lewis Acids and Wavelengths



investigated low abundant molecular ion signals. The difficult experimental conditions explain the observed relative experimental errors of about 15−20 ppm (absolute experimental errors in the range of 3−5 mmu). Infrared spectra were recorded with a Fourier transform (FT-IR) spectrometer. Irradiation experiments were carried out in a Luzchem CCP-4 V reactor using 14 coated low-pressure mercury lamps (λ = 300 and 350 nm, respectively).

General Procedure (GP) for Photoredox-Catalyzed Tetrahydrofuran Addition to Carbonyl Compounds. Argon gas was passed through a mixture of 0.75 mmol (1 equiv) of ketone in 6 mL of the ether (tetrahydrofuran, tetrahydropyran, or 1,4-dioxane) containing 0.5 equiv of titanium isopropoxide and 1 equiv of $BF_3{\cdot}Et_2O$ for 15 min. The degassed solution was irradiated with UV-A light (350 ± 30 nm) for 48 h at room temperature. After irradiation, the solution was poured into water and extracted three times with CH_2Cl_2. The organic phase was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residual was purified via column chromatography.

*1-(Tetrahydrofuran-2-yl)-1-phenylethanol (**3a**).*[13] The crude product prepared by GP from 0.75 mmol of acetophenone and tetrahydrofuran was purified by column chromatography [*c*-Hex/EtOAc (20:1)]; 126 mg, 87% yield. *erythro*-**3a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.35−1.45 (m, 1H), 1.62 (s, 3H), 1.56−1.68 (m, 1H), 1.73−1.82 (m, 2H), 2.58 (s, 1H), 3.80−3.94 (m, 2 H), 4.03−4.08 (m, 1H), 7.24 (d, J = 7.3 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.43 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 26.4, 26.5, 28.8, 69.5, 74.6, 85.9, 125.0,126.7, 128.1,145.0; IR (film) ν (cm^{-1}) = 3464, 2977, 2874, 1772, 1773, 1684, 1602, 1496, 1447, 1371, 1177, 1064, 1027, 760, 700, 640; GC-MS τ_R = 10.88 min, m/z (%) 192 (1, $[M]^+$), 174 (3, $[M - H_2O]^+$), 121 (100), 105 (20), 77 (22), 71 (28); CI m/z (%) 175 (37, $[M - OH]^+$), 121 (100), 105 (47), 91 (36), 77 (28), 51 (18). *threo*-**3a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.46 (s, 3H), 1.84−1.93 (m, 4H), 2.63 (s, 1H), 3.73−3.87 (m, 2H), 4.18 (t, J = 7.1 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 25.8, 26.3, 26.5, 69.2, 75.1, 85.6, 125.2, 126.9, 128.6, 146.7; IR (film) ν (cm^{-1}) = 3462, 2975, 2873, 1770, 1770, 1684, 1602, 1496, 1447, 1371, 1177, 1064, 1027, 760, 700, 640; GC-MS τ_R = 11.11 min, m/z (%) 192 (1, $[M]^+$), 174 (8, $[M - H_2O]^+$), 121 (100), 105 (20), 91 (11), 77 (27), 71 (32); CI m/z (%) 175 (39, $[M - OH]^+$), 121 (100), 105 (42), 91 (40), 77 (28), 51 (18).

*(Tetrahydrofuran-2-yl)diphenylmethanol (**3b**).*[19] The crude product prepared by GP from 0.75 mmol of benzophenone and tetrahydrofuran was purified by column chromatography [*c*-Hex/EtOAc (10:1)]; 68 mg, 36% yield. colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.44−1.63 (m, 1H), 1.75−1.96 (m, 3H), 3.02 (s, 1H), 3.82−4.02 (m, 2H), 4.87 (t, J = 7.2 Hz, 1H), 7.12−7.35 (m, 6H), 7.36−7.44 (m, 2H), 7.53−7.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 26.3, 26.9, 69.9, 78.4, 83.0, 125.6, 126.7, 127.0, 127.1, 128.1, 128.2, 144.5, 146.7; IR (film) ν (cm^{-1}) = 3462, 3059, 3026, 2977, 2872, 1710, 1599, 1493, 1448, 1361, 1171, 1066, 748, 697, 636; GC-MS τ_R = 13.95 min, m/z (%) 236 (9, $[M - H_2O]^+$), 180 (34), 165 (18), 130 (19), 105 (100); CI m/z (%) 237 (100, $[M - OH]^+$), 131 (33), 105 (89), 91 (36).

*Phenyl(tetrahydrofuran-2-yl)methanol (**3c**).*[16] The crude product prepared by GP from 0.75 mmol of benzaldehyde and tetrahydrofuran, was purified by column chromatography [*c*-Hex/EtOAc (8:1)]; 29 mg, 19% yield. *erythro*-**3c**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.59−1.75 (m, 2H), 1.81−1.98 (m, 2H), 2.96 (s, 1H), 3.82−3.93 (m, 2H), 3.97−4.05 (m, 1H), 4.45 (d, J = 7.5 Hz, 1H), 7.29−7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 26.1, 27.9, 68.4, 76.6, 83.4, 127.0, 128.0, 128.4, 140.7; IR (film) ν (cm^{-1}) = 3676, 3427, 2972, 2873, 1724, 1453, 1197, 1057, 760, 700; GC-MS τ_R = 11.00 min, m/z (%) 160 (1, $[M - H_2O]^+$), 107 (12), 79 (37), 71 (100). *threo*-**3c**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.62−1.69 (m, 2H), 1.78−1.91 (m, 2H), 2.52 (s, 1H), 3.77−3.87 (m, 2H), 4.12−4.06 (m, 1H), 4.94 (d, J = 3.7 Hz, 1H), 7.23−7.29 (m, 1H), 7.31−7.39 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 24.9, 26.2, 69.2, 74.2, 83.2, 126.1, 127.6, 128.4, 140.6; IR (film) ν (cm^{-1}) = 3676, 3427, 2972, 2873, 1724, 1453, 1197, 1057, 760, 700; GC-MS τ_R = 11.06 min, m/z (%) 160 (1, $[M - H_2O]^+$), 107 (11), 79 (43), 71 (100).

*1-(Tetrahydrofuran-2-yl)-1-(p-tolyl)ethan-1-ol (**3d**).*[13] The crude product prepared by GP from 0.75 mmol of 4′-methylacetophenone and tetrahydrofuran was purified by column chromatography [*c*-Hex/EtOAc (20:1)]; 103 mg, 67% yield. *erythro*-**3d**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.36−1.47 (m, 1H), 1.60 (s, 3H), 1.54−1.69 (m, 1H), 1.70−1.87 (m, 2H), 2.33 (s, 3H), 2.51 (s, 1H), 3.78−3.99 (m, 2H), 4.04 (dd, J = 8.1, 6.9 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 21.1, 26.4, 26.5, 28.8, 69.5, 74.4, 85.9, 124.9, 128.9, 136.2, 142.1; IR (film) ν (cm^{-1}) = 3469, 2976, 2872, 1775, 1682, 1607, 1515, 1451, 1370, 1180, 1068, 1046, 920, 815, 723; GC-MS τ_R = 11.53 min, m/z (%) 189 (17, $[M - OH]^+$), 145 (22), 135 (100), 119 (19), 106 (11), 91 (23); CI m/z (%) 189 (100, $[M - OH]^+$), 119 (78). *threo*-**3d**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.48 (s, 3H), 1.79−2.02 (m, 4H), 2.36 (s, 3H), 2.68 (s, 1H), 3.71−4.01 (m, 2H), 4.20 (t, J = 7.1 Hz), 7.19 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 21.1, 25.8, 26.2, 26.4, 69.1, 74.9, 85.6, 125.1, 128.9, 136.3, 143.8; IR (film) ν (cm^{-1}) = 3443, 2977, 2870, 1512, 1447, 1372, 1184, 1071, 1051, 918, 815, 728; GC-MS τ_R = 11.74 min, m/z (%) 189 (25, $[M - OH]^+$), 145 (21), 135 (100), 118 (21), 91 (14); CI m/z (%) 189 (100, $[M - OH]^+$), 119 (78).

*1-(Tetrahydrofuran-2-yl)-1-(m-tolyl)ethan-1-ol (**3e**).* The crude product prepared by GP from 1 mmol of 3′-methylacetophenone and tetrahydrofuran was purified by column chromatography [*c*-Hex/EtOAc (25:1→20:1)]; 136 mg, 66% yield. *erythro*-**3e**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.37−1.47 (m, 1H), 1.61 (s, 3H), 1.56−1.69 (m, 1H), 1.74−1.84 (m, 2H), 2.36 (s, 3H), 2.47 (s, 1H), 3.77−4.00 (m, 2H), 4.06 (dd, J = 8.2, 6.9 Hz, 1H), 7.04−7.08 (m, 1H),

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7.20−7.22 (m, 2H), 7.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 21.8, 26.4, 26.6, 29.0, 69.5, 74.6, 85.9, 122.1, 125.7, 127.5, 128.1, 137.7, 144.9; IR (film) ν (cm^{-1}) = 3676, 3476, 2976, 1607, 1451, 1375, 1233, 1167, 1067, 1056, 787, 707; GC-MS τ_R = 11.49 min, *m*/*z* (%) 188 (73, $[M - H_2O]^+$), 135 (100), 117 (47), 91 (50); CI *m*/*z* (%) 189 (100, $[M - OH]^+$), 119 (16). *threo*-**3e**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.44 (s, 3H), 1.84−1.94 (m, 4H), 2.36 (s, 3H), 2.63 (s, 1H), 3.74−3.87 (m, 2H), 4.18 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 6.9 Hz, 1H), 7.18−7.40 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 21.4, 25.4, 25.8, 26.1, 68.7, 74.5, 85.2, 121.8, 125.4, 127.2, 127.7, 137.3, 146.4; IR (film) ν (cm^{-1}) = 3443, 2978, 2868, 1608, 1458, 1372, 1172, 1073, 927, 788, 706; GC-MS τ_R = 11.68 min, *m*/*z* (%) 188 (99, $[M - H_2O]^+$), 173 (47), 145 (58), 135 (100), 117 (78), 91 (47); CI *m*/*z* (%) 189 (100, $[M - OH]^+$), 119 (17).

1-(4-Fluorophenyl)-1-(tetrahydrofuran-2-yl)ethan-1-ol (**3h**). The crude product prepared by GP from 1 mmol of 4′-fluoroacetophenone and tetrahydrofuran was purified by column chromatography [*c*-Hex/EtOAc (20:1)]; 173 mg, 82% yield. *erythro*-**3h**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.40−1.46 (m, 1H, H-7), 1.63 (s, 3H), 1.59−1.64 (m, 1H), 1.77−1.87 (m, 2H), 2.52 (s, 1H), 3.84−3.97 (m, 2H), 4.05 (dd, *J* = 8.4, 6.8 Hz), 7.00−7.07 (m, 2H), 7.39−7.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 26.2, 26.4, 28.7, 69.4, 74.3, 85.7 ($^6J_{F,C}$ = 0.9 Hz), 114.8 ($^2J_{F,C}$ = 21.1 Hz),126.6 ($^3J_{F,C}$ = 7.8 Hz),140.6 ($^4J_{F,C}$ = 3.2 Hz), 161.7 ($^1J_{F,C}$ = 244.7 Hz); IR (film) ν (cm^{-1}) = 3679, 3471, 2977, 2901, 1603, 1511, 1408, 1392, 1375, 1224, 1160, 1067, 1048, 837; GC-MS τ_R = 10.92 min, *m*/*z* (%) 192 (49, $[M - H_2O]^+$), 139 (100), 123 (40), 71 (24); CI *m*/*z* (%) 193 (100, $[M - OH]^+$), 123 (26). *threo*-**3h**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.44 (s, 3H), 1.83−1.92 (m, 4H), 2.62 (s, 1H), 3.74−3.87 (m, 2H), 4.11−4.16 (m, 1H), 6.93−7.15 (m, 2H), 7.36−7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 25.7, 25.8, 26.0, 69.2, 74.8, 85.5, 114.9 ($^2J_{F,C}$ = 21.1 Hz),127.0 ($^3J_{F,C}$ = 7.9 Hz),142.5 ($^4J_{F,C}$ = 3.1 Hz), 161.9 ($^1J_{F,C}$ = 244.8 Hz); IR (film) ν (cm^{-1}) = 3448, 2980, 2873, 1607, 1509, 1375, 1225, 1162, 1074, 837; GC-MS τ_R = 11.16 min, *m*/*z* (%) 192 (38, $[M - H_2O]^+$), 139 (100), 123 (29), 71 (31); CI *m*/*z* (%) 193 (100, $[M - OH]^+$), 139 (30), 123 (35).

1-(2-Fluorophenyl)-1-(tetrahydrofuran-2-yl)ethan-1-ol (**3i**). The crude product prepared by GP from 0.75 mmol of 2′-fluoroacetophenone and tetrahydrofuran was purified by column chromatography [*c*-Hex/EtOAc (20:1)]; 66 mg, 42% yield. *erythro*-**3i**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.39−1.62 (m, 2H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.75−1.94 (m, 2H), 2.77 (s, 1H), 3.91 (h, *J* = 8.1 Hz, 2H), 4.41 (ddd, *J* = 8.3, 7.1, 3.4 Hz, 1H), 6.98 (ddd, *J* = 12.0, 8.0, 1.2 Hz, 1H), 7.14 (td, *J* = 7.6, 1.3 Hz, 1H), 7.22 (ddd, *J* = 9.8, 4.7, 2.1 Hz, 1H), 7.71 (td, *J* = 7.8, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 26.5, 26.8, 27.8 ($^5J_{F,C}$ = 3.3 Hz), 69.5, 73.8 ($^4J_{F,C}$ = 4.9 Hz), 83.3 ($^5J_{F,C}$ = 5.4 Hz), 115.7 ($^3J_{F,C}$ = 23.6 Hz), 124.2 ($^4J_{F,C}$ = 2.7 Hz), 127.7 ($^3J_{F,C}$ = 5.1 Hz), 128.7 ($^3J_{F,C}$ = 8.3 Hz), 132.1 ($^2J_{F,C}$ = 39.8 Hz, C-2), 159.3 ($^1J_{F,C}$ = 245.0 Hz); IR (film) ν (cm^{-1}) = 3461, 2978, 2873, 1685, 1615, 1581, 1486, 1450, 1371, 1212, 1068, 1032, 757; GC-MS τ_R = 10.58 min, *m*/*z* (%) 193 (21, $[M - OH]^+$), 162 (13), 145 (32), 139 (100), 123 (44), 109 (18), 71 (18); CI *m*/*z* (%) 193 (100, $[M - OH]^+$), 123 (56). *threo*-**3i**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.52 (d, *J* = 1.6 Hz, 3H), 1.86−2.04 (m, 4H), 2.94 (s), 3.70−3.80 (m, 1H), 3.83−3.88 (m, 1H), 4.38 (t, *J* = 7.8 Hz, 1H), 7.00 (ddd, *J* = 12.3, 8.1, 1.3 Hz, 1H), 7.13 (td, *J* = 7.6, 1.3 Hz, 1H), 7.20−7.25 (m, 1H), 7.60, (td, *J* = 8.1, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 23.9 ($^5J_{F,C}$ = 4.4 Hz), 26.0, 26.2, 69.1, 73.9 ($^4J_{F,C}$ = 3.7 Hz), 84.0 ($^5J_{F,C}$ = 5.0 Hz), 116.1 ($^3J_{F,C}$ = 25.4 Hz), 124.2 ($^4J_{F,C}$ = 3.3 Hz), 127.4 ($^3J_{F,C}$ = 4.6 Hz), 128.9 ($^3J_{F,C}$ = 8.6 Hz), 134.0 ($^2J_{F,C}$ = 10.8 Hz), 159.5 ($^1J_{F,C}$ = 239.2 Hz); IR (film) ν (cm^{-1}) = 3457, 2981, 2946, 2876, 1614, 1580, 1484, 1449, 1377, 1273, 1207, 1070, 920, 818, 758; GC-MS τ_R = 11.50 min, CI *m*/*z* (%) 193 (100, $[M - OH]^+$), 123 (56).

1-(4-Chlorophenyl)-1-(tetrahydrofuran-2-yl)ethan-1-ol (**3k**). The crude product prepared by GP from 1 mmol of 4′-chloroacetophenone and tetrahydrofuran was purified by column chromatography [*c*-Hex/EtOAc (10:1)]; 144 mg, 64% yield. *erythro*-**3k**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.35−1.46 (m, 1H), 1.59 (s, 3H), 1.54−1.64 (m, 1H), 1.72−1.88 (m, 2H), 2.53 (s, 1H), 3.78−3.97 (m, 2H), 4.02 (dd, *J* = 8.3, 6.8 Hz), 7.24−7.33 (m, 2H), 7.33−7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 26.4, 26.5, 28.8, 69.5, 74.4, 85.7, 126.6, 128.3, 132.6, 143.5; IR (film) ν (cm^{-1}) = 3676, 3463, 2975, 2904, 1494, 1403, 1067, 1048, 835 cm^{-1}; GC-MS τ_R = 12.22 min, *m*/*z* (%) 229 (8,$[M + H]^+$]), 227(9, $[M + H]^+$]), 182 (16), 180 (18), 118 (41), 102 (100), 90 (35), 75 (59), 50 (32); CI *m*/*z* (%) 211 (30, $[M - OH]^+$), 209 (100, $[M - OH]^+$), 139 (14). *threo*-**3k**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.44 (s, 3H), 1.81−1.97 (m, 4H), 2.57 (s, 1H), 3.69−3.93 (m, 2H), 4.11−4.16 (m, 1H), 7.27−7.35 (m, 2H), 7.38−7.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) = 26.4, 26.7, 26.9, 69.7, 75.2, 85.9, 127.2, 128.8, 133.2, 145.8; IR (film) ν (cm^{-1}) = 3676, 3448, 2979, 2899, 1491, 1394, 1228, 1075, 1053, 833; GC-MS τ_R = 12.61 min, *m*/*z* (%) 200 (60), 198 (60), 183 (43), 185 (48), 157 (17), 120 (20), 102 (22), 91 (100), 77 (50), 65 (21), 50 (31); CI *m*/*z* (%) 211 (12, $[M - OH]^+$), 209 (100, $[M - OH]^+$), 139 (16).

1-(4-Bromophenyl)-1-(tetrahydrofuran-2-yl)ethan-1-ol (**3l**). The crude product prepared by GP from 1 mmol of 4′-bromoacetophenone and tetrahydrofuran was purified by column chromatography [*c*-Hex/EtOAc (20:1→8:1)]; 15 mg, 6% yield. *erythro*-**3l**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.40−1.47 (m, 1H), 1.61 (s, 3H), 1.58−1.64 (m, 1H), 1.78−1.87 (m, 2H), 2.52 (s, 1H), 3.85−3.96 (m, 2H), 4.04 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.32−7.36 (m, 2H), 7.46−7.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 26.4, 26.5, 28.8, 69.6, 74.5, 85.6, 120.8, 127.0, 131.3, 144.1; IR (film) ν (cm^{-1}) = 3676, 3473, 2975, 2091, 1679, 1592, 1489, 1395, 1251, 1198, 1067, 1009, 919, 894, 835; GC-MS τ_R = 12.71 min, *m*/*z* (%) 254 (32, $[M - H_2O]^+$), 252 (36, $[M - H_2O]^+$), 201 (89), 199 (87), 192 (100), 146 (35), 71 (47).

1-(2-Methoxyphenyl)-1-(tetrahydrofuran-2-yl)ethan-1-ol (**3n**). The crude product prepared by GP from 0.75 mmol of 2′-methoxyacetophenone was purified by column chromatography [*c*-Hex/EtOAc (20:1)]; 37 mg, 22% yield. *erythro*-**3n**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.45−1.59 (m, 2H), 1.63 (s, 3H), 1.71−1.88 (m, 2H), 3.24 (brs, 1H), 3.82 (s, 3H), 3.84−3.95 (m, 2H), 4.56 (t, *J* = 6.1 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.91−7.02 (m, 1H), 7.16−7.30 (m, 1H), 7.63 (d, *J* = 9.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 26.2, 26.6, 26.7, 55.3, 69.4, 75.0, 83.3, 111.0, 120.9, 127.2, 128.2, 133.3, 156.1; IR (film) ν (cm^{-1}) = 3676, 3513, 2973, 2872, 1713, 1600, 1583, 1488, 1463, 1436, 1236, 1182, 1057, 1026, 754 cm^{-1}; GC-MS τ_R = 11.98 min, *m*/*z* (%) 205 (3, $[M - OH]^+$), 189 (3), 151 (68), 133 (29), 105 (100), 79 (17), 55 (11); CI *m*/*z* (%) 205 (100, $[M - OH]^+$), 161 (26), 135 (22), 97 (21). *threo*-**3n**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.52 (s, 3H), 1.82−1.95 (m, 4H), 3.72−3.83 (m, 2H), 3.85 (s, 3H), 4.48−4.53 (m, 1H), 6.88−7.01 (m, 2H), 7.20−7.26 (m, 1H), 7.47−7.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 23.3, 26.4, 26.5, 55.5, 69.0, 75.6, 83.7, 111.6, 121.0, 126.9, 128.4, 134.5, 156.5; IR (film) ν (cm^{-1}) = 3673, 3512, 2971, 2870, 1713, 1600, 1581, 1485, 1460, 1437, 1229, 1180, 1057, 1026; GC-MS τ_R = 12.25 min, *m*/*z* (%) 204 (2, $[M - H_2O]^+$), 189 (11), 151 (37), 133 (23), 121 (22), 105 (100), 91 (15), 79 (13); CI *m*/*z* (%) 205 (100, $[M - OH]^+$), 161 (26), 135 (22), 97 (21).

1-(4-Dioxan-2-yl)-1-phenylethan-1-ol (**5a**). The crude product prepared by GP from 0.75 mmol of acetophenone and 1,4-dioxane was purified by column chromatography [*c*-Hex/EtOAc (20:1)]; 20 mg, 13% yield. The pinacol from acetophenone was formed as side product (24 mg, 26% yield). *erythro*-**5a**: colorless crystals; mp 71−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.60 (s, 3H), 2.70 (s, 1H), 3.24 (dd, *J* = 11.7, 2.6 Hz, 1H), 3.41 (dd, *J* = 11.6, 10.3 Hz, 1H), 3.47−3.58 (m, 1H), 3.60−3.72 (m, 2H), 3.77−3.92 (m, 2H), 7.22−7.30 (m, 1H), 7.30−7.38 (m, 2H), 7.40−7.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 28.0, 66.2, 67.0, 67.4, 74.3, 80.6, 124.9, 127.2, 128.4, 143.4; GC-MS τ_R = 11.56 min, *m*/*z* (%) 146 (100), 121 (81), 105 (41), 91 (19), 79 (21), 77 (44); CI *m*/*z* (%) 191 (2, $[M - OH]^+$), 147 (11), 129 (61), 105 (100), 91 (19), 79 (14).

1-Phenyl-1-(tetrahydro-2H-pyran-2-yl)ethan-1-ol (**6a**).[20] The crude product prepared by GP from 1 mmol of acetophenone and tetrahydropyran was purified by column chromatography [*c*-Hex/EtOAc (15:1)]; 52 mg, 25% yield. *erythro*-**6a**: colorless crystals; mp 55−57 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.03−1.13 (m, 1H), 1.20−1.53 (m, 5H), 1.58 (s, 3H), 1.71−1.79 (m, 1H), 2.81 (s, 1H), 3.37−3.40 (m, 1H), 3.46−3.60 (m, 1H), 4.02−4.15 (m, 1H), 7.20−7.25 (m, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.37−7.45 (m, 2H); ^{13}C NMR (125

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MHz, $CDCl_3$) δ (ppm) = 23.4, 25.4, 26.1, 27.8, 69.2, 75.6, 83.8, 125.4, 126.6, 128.1, 144.8; IR (film) ν (cm^{-1}) = 3559, 3484, 3092, 3059, 3030, 2936, 2855, 1494, 1448, 1371, 1209, 1178, 1088, 1063, 1029, 897, 701; GC-MS τ_R = 11.43 min, m/z (%) 188 (58, $[M - H_2O]^+$), 173 (24), 144 (51), 129 (47), 105 (55), 85 (100), 77 (56), 67 (52); CI m/z (%) 189 (28, $[M - OH]^+$), 121 (43), 105 (74), 77 (92), 67 (100), 51 (33). *threo*-**6a**: colorless crystals; mp 90−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.47 (s, 3H), 1.32−1.62 (m, 5H), 1.73−1.92 (m, 1H), 3.12 (s, 1H), 3.32−3.54 (m, 2H), 3.92−4.09 (m, 1H), 7.18−7.28 (m, 1H), 7.33−7.36 (m, 2H), 7.44−7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 23.5, 23.5, 25.8, 26.1, 69.1, 75.9, 84.3, 125.9, 126.9, 128.1, 145.9; IR (film) ν (cm^{-1}) = 3671, 3476, 3087, 3056, 2938, 2855, 1726, 1496, 1447, 1376, 1207, 1089, 1045, 893, 765; GC-MS τ_R = 11.63 min, m/z (%) 188 (76, $[M - H_2O]^+$), 173 (30), 144 (100), 129 (86), 105 (67), 85 (75), 77 (61), 67 (57); CI m/z (%) 121 (37), 105 (66), 77 (100), 67 (95), 51 (32). Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.69; H, 8.80. Found: C, 75.16; H, 8.43.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01085. The crystal data for the three structures *threo*-**6a**, *erythro*-**6a**, and *erythro*-**5a** were deposited at the CCDC with the following numbers: *threo*-**6a**, CCDC 1477826; *erythro*-**6a**, CCDC 1477824; *erythro*-**5a**, CCDC 1477825.

Crystal structure of *erythro*-**5a** (CIF)
Crystal structure of *erythro*-**6a** (CIF)
Crystal structure of *threo*-**6a** (CIF)
NMR spectra (^{1}H and ^{13}C) of all (separated) erythro/threo diastereo-isomeric products and thermal ellipsoid plots for the X-ray diffraction structures, information on the crystal structure determination, crystal parameters, and refinement metrics (PDF)

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Notes

The authors declare no competing financial interest.

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