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Note

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Selective C−H Activation of Methoxy Groups in a Three-Component Photoreaction

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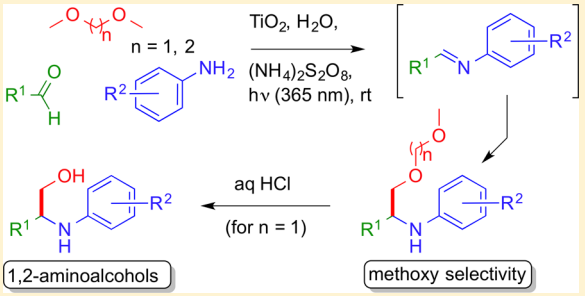
Supporting Information

ABSTRACT: Surprisingly, the photocatalytic activation of ethers by H-abstraction and addition of the generated radicals to iminium ions formed in situ from aldehydes and anilines predominantly yielded the products of methoxy activation for dimethoxymethane and 1,2-dimethoxyethane. Various anilines and aromatic as well as aliphatic aldehydes are suitable reaction partners for this three-component photoreaction (Porta-type process) which also provides a simple access to 1,2-aminoalcohols.

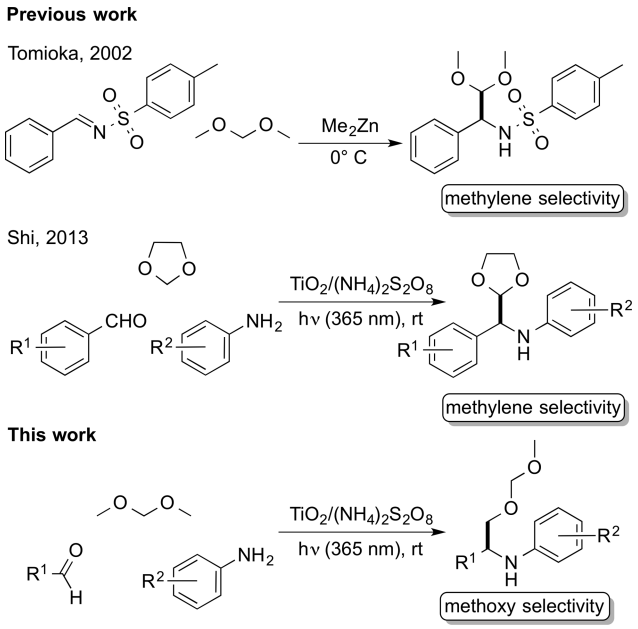


Regioselectivity is an important goal in organic synthesis. In particular, manipulations of unactivated C−H bonds are highly attractive elements for step economic syntheses and currently represent one of the most active research fields in organic chemistry.[1−7] The growing demand for waste and resources minimization calls for new and efficient processes utilizing abundantly available building blocks. Multicomponent reactions[8−15] or modular one-pot syntheses which comprise a regioselective activation of an unactivated C−H bond may fulfill these criteria. Here, we report a simple one-pot procedure for the light-induced coupling reaction of dimethoxymethane (DMM) or 1,2-dimethoxyethane (DME) with anilines and aldehydes. The products resulting from DMM can be easily transformed into 1,2-aminoalcohols, which are key elements of a wide variety of bioactive compounds.[16]

In the course of our work on protoberberine alkaloids,[17] we were in need of a facile synthesis of α-aminoaldehydes. The photochemical version of the Porta-type reaction[18−21] of anilines, benzaldehydes, and 1,3-dioxolane reported by Shi et al.[22] appeared attractive as it provides *N*-[1,3-dioxolan-2-yl(aryl)methyl]anilines, protected α-aminoaldehydes, in a single operation. When 1,3-dioxolane was replaced by DMM in the expectation to obtain the dimethyl acetal of an α-aminoaldehyde, the product of methoxy activation was surprisingly obtained as the major regioisomer. The same unexpected observation was made for 1,2-dimethoxyethane. In most cases, the isomeric ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixtures was higher than anticipated statistically (3:1 for DMM, 3:2 for DME). Remarkably, previous reports on the radical addition of DMM to *N*-sulfonylimines (Scheme 1) or of DME to electron-deficient nitrogen heterocycles all describe selectivity for the methylene position.[22−24]

The course of the reaction presumably involves H-abstraction from the methoxy group of the ether by the TiO_2 photocatalyst[25] or sulfate radicals generated by persulfate cleavage. The resulting alkoxymethylene radicals are nucleophilic due to

Scheme 1. Radical Addition of Dimethoxymethane to Imines



overlap of the SOMO with the lone pairs at oxygen and preferably add to the electron-deficient C═N bond of iminium ions formed in situ from the aldehyde and the amine component (Scheme 2).[26]

While both TiO_2 and UV irradiation turned out to be necessary, the persulfate additive could be omitted at the expense of the reaction rate.[22] To explore the scope of the photochemical three-component reaction, various amines and aldehydes were

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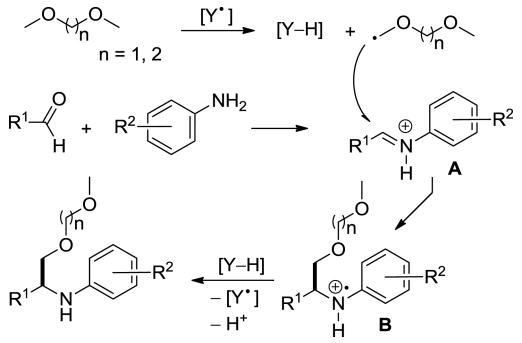
Scheme 2. Proposed Reaction Mechanism



reacted with an aqueous solution of DMM (1:1) containing TiO_2 and $(NH_4)_2S_2O_8$ under UV irradiation (365 nm) in a sealed tube (argon) at room temperature (Table 1).

The products of the methoxy activation could be obtained in moderate to high yields of 52−87%. For compounds **7**−**9**, the minor regioisomer resulting from methylene activation could not be removed by chromatography. 2-Aminophenol (**1g**) or 4-(dimethylamino)benzaldehyde (**2d**) were no suitable substrates for the three-component reaction under identical conditions. In the case of **1g** (entry 8), no imine formation was detected under the reaction conditions (^{1}H NMR) and decomposition occurred presumably due to the tendency of the amine component to undergo one-electron oxidation. For aldehyde **2c**, steric hindrance might have led to a significant reduction of the reaction rate. Compounds **1b** and **2d** formed the required imine, but no radical addition took place, possibly due an unfavorably high electron density (entry 10). While moderate to high yields were obtained for the reaction of anilines, aliphatic amines failed to give the expected products of radical addition. The lacking stabilization of the aminium radical cation **B** (Scheme 2) resulting from C−C bond formation could account for this behavior. In extension of the scope reported by Shi et al.,[22] aliphatic aldehydes can also be employed, although the use of unbranched representatives like pentanal resulted in complex mixtures (Table 1, entry **2f**). The photochemical three-component Porta-type reaction with DME is also efficient and provided the products of methoxy activation in moderate to good yields of 38−64% under identical conditions. The results are summarized in Table 2.

The reaction works for the same starting materials as used in combination with DMM. Compared to the products of Table 1, the regioisomeric ratios in Table 2 are lower. This might be due to the statistical effect combined with a smaller difference in accessibility in the H-abstraction and stability as well as reactivity for the two radical species formed from DME.

In the case of the reaction with DMM, the methoxy activation provides a simple access to 1,2-aminoalcohols, which are, e.g., an important compound class in medicinal chemistry.[27,28] In comparison to many other methods for their synthesis,[29−38] nucleophilic radical hydroxymethylations of imines can be a simple and cheap alternative.[18,39−42] In our case, the MOM-group can be removed from the addition products with aqueous HCl in THF at 60 °C. The corresponding aminoalcohols **20a** and **20b** were obtained over two steps in yields of 48% and 42%, respectively (Scheme 3).

In summary, the photochemical Porta-type addition of open chain ethers such as DME and DMM to in situ formed imines was found to show a surprising selectivity for the C−H activation at the methoxy group. The use of MTBE or anisole as alternative methoxy-functionalized ether substrates only led to very low conversion under identical conditions as judged by HPLC/MS instead. Currently, we have no experimental evidence as to whether the observed regioselectivity for DMM and DME is due to a preference of the photogenerated H-abstracting species (vide supra) for the sterically less hindered methoxy H atoms or to the reported instability of the dimethoxymethyl radical generated from DMM.[43] However, no products resulting from methyl radicals generated in the fragmentation of the dimethoxymethyl radical to methyl formate were found. As the latter radical is more nucleophilic than its (methoxymethoxy)methyl isomer, the rate of its reaction with electron-deficient iminium ions should be higher. Preliminary calculations at the UB3LYP/6-311G(2d,p) level of theory (data not shown) indicated the dimethoxymethyl radical to be more stable by about 4.7 kcal/mol. An interconversion of the less stable, less nucleophilic to the more stable, more nucleophilic radical by H-abstraction from another molecule of DMM might explain why more electrophilic iminium species such as those derived from **1c** or **1d** show higher selectivity for the products of methoxy activation. In the case of less reactive iminium salts, longer radical lifetimes would favor this interconversion. This, however, would require an as yet unseen preference for initial H-abstraction at the methoxy group but could explain the complementary behavior compared to known radical functionalizations of the same radical precursor.[23] The reported three-component reaction is robust and uses only cheap and readily available starting materials and reagents. Being one of the very rare cases of a C−H functionalization at methoxy groups,[44,45] it permits the synthesis of β-aminoethers in a single operation with 100% atom economy and can be used to produce β-aminoalcohols in an additional step.

EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial suppliers without further purification. Anhydrous DME was distilled from potassium/benzophenone under argon. Melting points were determined in open capillary tubes. NMR spectra were recorded with a 300 MHz spectrometer (300 MHz ^{1}H and 75.5 MHz ^{13}C), a 400 MHz (400 MHz ^{1}H and 100.6 MHz ^{13}C), or with a 600 MHz spectrometer (600 MHz ^{1}H and 151 MHz ^{13}C) with digital architecture and equipped with 5 mm probes. The δ values are reported in parts per million (ppm) downfield from TMS and were referenced to the residual solvent signal ($CHCl_3$, 7.26 ppm). Coupling constants J are given in Hertz (Hz). IR spectra were recorded using a diamond ATR unit and are reported in terms of frequency of absorption (ν, cm^{-1}). ESI-HRMS spectra were recorded on a Q-TOF instrument with a dual source and a suitable external calibrant. Preparative thin-layer chromatography was carried out on 2 mm silica gel plates with a fluorescence indicator. Substance bands were detected by illumination with UV light (254 and 360 nm).

General Experimental Procedure for the Addition Reactions. TiO_2 (20 mg, 0.25 mmol, 1.3 equiv) and $(NH_4)_2S_2O_8$ (6.0 mg, 0.026 mmol, 0.13 equiv) were dispersed in a mixture of water (2.5 mL) and the respective ether (2.5 mL). After the addition of aldehyde (0.30 mmol, 1.5 equiv) and amine (0.20 mmol), the reaction mixture was degassed by argon, bubbling for 1 min and stirred for 20 h under UV-A irradiation (400 W Hg-lamp, 350−375 nm) at room temperature. The mixture was filtered, and the filter cake was washed with DCM (40 mL) and ethyl acetate (40 mL). The combined filtrates were concentrated *in vacuo*, and the resulting crude product was purified by chromatography unless otherwise noted.

*N-[2-(Methoxymethoxy)-1-phenylethyl]aniline (**3**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with aniline (**1a**, 18.6 mg, 0.20 mmol) and DMM (2.5 mL). After 20 h, purification by thin-layer chromatography (cyclohexane/AcOEt/NEt_3 = 7.0/2.5/0.5) afforded the title compound (33.4 mg, 65%) as a colorless oil.

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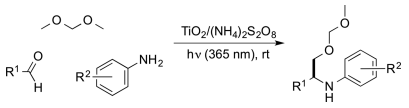
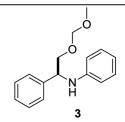
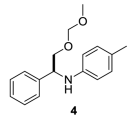
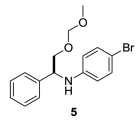
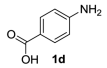
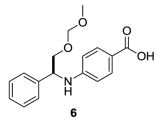
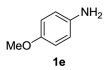
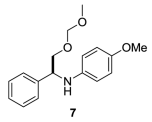
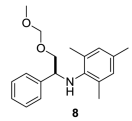
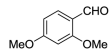
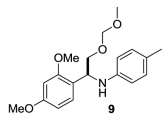
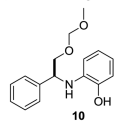
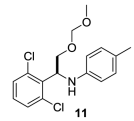
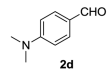
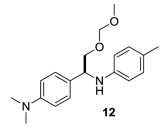
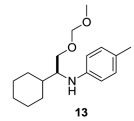
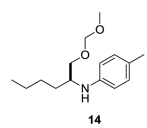
Table 1. Addition of DMM to Imines Formed in situ



Entry	Aniline	Benzaldehyde	Product	Yield[a]	Isomeric ratio[d]
1	 1a	 2a	 3	66%	4.5:1
2	 1b	 2a	 4	72%	4.5:1
3	 1c	 2a	 5	58%	5.9:1
4	 1d	 2a	 6	87%	12.5:1
5	 1e	 2a	 7	75%[b]	4.2:1
6	 1f	 2a	 8	77% [b]	4.2:1
7	 1b	 2b	 9	71%[b]	3.0:1
8	 1g	 2a	 10	[c]	
9	 1b	 2c	 11	traces	
10	 1b	 2d	 12	[c]	
11	 1b	 2e	 13	52%	2.8:1
12	 1b	 2f	 14	[e]	

[a]Yields are those of products isolated by chromatography. [b]Minor regioisomeres could not be separated. [c]Product could not be detected via NMR or ESI-MS. [d]Regioisomeric ratio of methoxy vs methylene activation determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [e]Complex mixture.

R_f = 0.60 (cyclohexane/AcOEt/Et_3N = 7.5/2.0/0.5). IR (ATR): 3397 (m, br), 2948 (s, sh), 2887 (m), 1733 (m), 1603 (s), 1505 (s), 1109 (s), 1036 (s), 751 (s), 701 (s). ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ = 7.45−7.39 (m, 2H, H-2″, H-6″), 7.37−7.29 (m, 2H, H-3″, H-5″), 7.28−7.24 (m, 1H, H-4″), 7.13−7.05 (m, 2H, H-3, H-5), 6.66 (tt, J = 7.4, 1.3 Hz, 1H, H-4), 6.57−6.51 (m, 2H, H-2, H-6), 4.68 (d, J = 6.6 Hz, 1H, OCH_2O),

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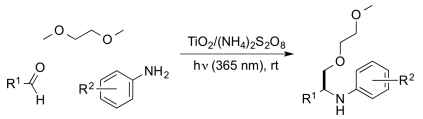
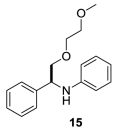
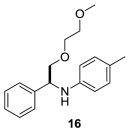
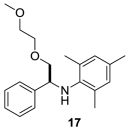
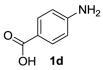
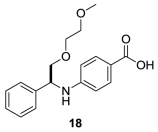
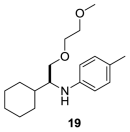
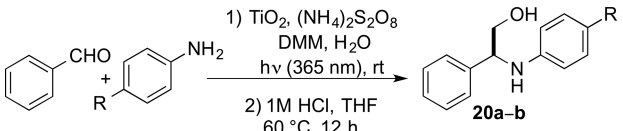
Table 2. Addition of DME to Imines Formed in situ



Entry	Aniline	Benzaldehyde	Product	Yield[a]	Isomeric ratio[b]
1	 1a	 2a	 15	61%	2.6:1
2	 1b	 2a	 16	64%	2.9:1
3	 1f	 2a	 17	43%	[c]
4	 1d	 2a	 18	52%	2.4:1
5	 1b	 2e	 19	38%	[c]

[a]Yields are those of products isolated by chromatography. [b]Regioisomeric ratio of methoxy vs methylene activation determined by ^{1}H NMR spectroscopy of the crude reaction mixture taking into account all stereoisomers. [c]Regioisomeric ratio could not be determined due to signal overlap in ^{1}H NMR.

Scheme 3. Preparation of 1,2-Aminoalcohols



a. R = CH_3, 48% over two steps
b. R = H, 42% over two steps

4.63 (d, J = 6.6 Hz, 1H, OCH_2O), 4.53 (dd, J = 8.0, 4.1 Hz, 1H, H-1′), 3.86 (dd, J = 10.4, 4.1 Hz, 1H, H$_a$-2′), 3.66 (dd, J = 10.4, 8.0 Hz, 1H, H$_b$-2′), 3.32 (s, 3H, OCH_3). ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ = 147.7 (C1), 140.7 (C1″), 129.2 (C3, C5), 128.8 (C3″, C5″), 127.6, (C4″), 126.9 (C2″, C6″), 117.8 (C4), 113.9 (C2, C6), 96.8 (OCH_2O), 72.5 (C2′), 58.4 (C1′), 55.6 (OCH_3). ESI-MS: m/z (%) = 258.1 (100) [M + H]$^+$. ESI-HRMS: calcd for [$C_{16}H_{20}NO_2$]$^+$: m/z = 258.1494, found: 258.1499.

*N-[2-(Methoxymethoxy)-1-phenylethyl]-4-methylaniline (**4**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with *p*-toluidine (**1b**, 21.4 mg, 0.20 mmol) and DMM (2.5 mL). After 20 h, purification by thin-layer chromatography (cyclohexane/AcOEt = 7/3) afforded the title compound (38.1 mg, 70%) as a pale yellow oil.

R_f = 0.51 (cyclohexane/AcOEt = 7/3). IR (ATR): 3395 (w, br), 2884 (m, sh), 2825 (m), 1733 (w), 1618 (m), 1520 (s), 1151 (m), 1108 (s), 1037 (s), 701 (m). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.44−7.38 (m, 2H, H-2″, H-6″), 7.35−7.29 (m, 2H, H-3″, H-5″), 7.26−7.22 (m, 1H, H-4″), 6.92−6.87 (XX′-part of a AA′XX′-system, 2H, H-3, H-5), 6.48−6.43 (AA′-part of a AA′XX′-system, 2H, H-2, H-6), 4.67 (d, J = 6.6 Hz, 1H, OCH_2O), 4.62 (d, J = 6.6 Hz, 1H, OCH_2O), 4.51 (s, 1H, NH), 4.50 (dd, J = 8.1, 4.1 Hz, 1H, H-1′), 3.84 (dd, J = 10.4, 4.1 Hz, 1H, H$_a$-2′), 3.64 (dd, J = 10.4, 8.1 Hz, 1H, H$_b$-2′), 3.31 (s, 3H, OCH_3), 2.18 (s, 3H, CH_3). ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ = 145.3 (C1), 140.8 (C1″), 129.7 (2C, C3, C5), 128.7 (2C, C3″, C5″), 127.5 (C4″), 127.0 (C4), 126.9 (2C, C2″, C6″), 114.1 (2C, C2, C6), 96.7 (OCH_2O), 72.6 (C2′), 58.6 (C1′), 55.6 (OCH_3), 20.5 (CH_3). ESI-MS: m/z (%) = 272.2 (100) [M + H]$^+$. ESI-HRMS: calcd for [$C_{17}H_{22}NO_2$]$^+$: m/z = 272.1651, found: 272.1656.

*4-Bromo-N-[2-(methoxymethoxy)-1-phenylethyl]aniline (**5**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with 4-bromoaniline (**1c**, 34.4 mg, 0.20 mmol) and DMM (2.5 mL). After 20 h, purification by thin-layer chromatography (cyclohexane/AcOEt/NEt$_3$ = 90/7/3) afforded the title compound (38.9 mg, 58%) as a colorless amorphous solid.

R_f = 0.40 (cyclohexane/AcOEt/Et$_3$N = 7.5/2.0/0.5). IR (ATR): 3395 (w, br), 2930 (m, sh), 2886 (m), 1732 (w), 1594 (m), 1496 (s), 1107 (m), 1108 (s) 1036 (s) 702 (m). ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ = 7.41−7.26 (m, 5H, 5 × Ar-H), 7.18−7.12 (XX′-part of a AA′XX′-system, 2H, H-3, H-5), 6.43−6.37 (AA′-part of a AA′XX′-system, 2H, H-2, H-6), 4.68 (s, 1H, NH), 4.67 (d, J = 6.6 Hz, 1H, OCH_2O), 4.62 (d, J = 6.6 Hz, 1H, OCH_2O), 4.48 (dd, J = 8.1, 4.0 Hz, 1H, H-1′), 3.86 (dd, J = 10.4, 4.0 Hz, 1H, H$_a$-2′), 3.64 (dd, J = 10.4, 8.1 Hz, 1H, H$_b$-2′), 3.31 (s, 3H, OCH_3). ^{13}C NMR, HMBC, HSQC (101 MHz, $CDCl_3$): δ = 146.5 (C1), 139.9 (C1″), 131.7 (2C, C3, C5), 128.7 (2C, C3″, C5″), 127.6 (C4″), 126.7 (2C, C2″, C6″), 115.4 (2C, C2, C3), 109.4 (C4), 96.7 (OCH_2O), 72.4 (C2′) 58.3 (C1′) 55.7 (OCH_3). ESI-MS: m/z (%) = 336.1 (100) [M + H]$^+$. ESI-HRMS: calcd for [$C_{16}H_{18}{}^{81}BrNO_2Na$]$^+$: m/z = 358.0419, found: 358.0421.

*4-{[2-(Methoxymethoxy)-1-phenylethyl]amino}benzoic Acid (**6**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with 4-aminobenzoic acid (**1d**, 27.4 mg, 0.20 mmol)

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and DMM (2.5 mL). After 20 h, the reaction mixture was filtered and washed with DCM (40 mL) and methanol (40 mL). The filtrate was concentrated *in vacuo*, and the resulting crude product was filtered through a short plug of silica to afford the title compound (52.4 mg, 87%) as a colorless amorphous solid.

R_f = 0.57 (AcOEt). IR (ATR): 3363 (w, br), 2940 (w, sh), 2886 (w), 1671 (m), 1604 (s), 1284 (m), 1175 (m), 1034 (m), 702 (w). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.86−7.80 (AA′-part of a AA′XX′-system, 2H, H-2, H-6), 7.40−7.31 (m, 4H, Ar-H), 7.30−7.25 (m, 1H, H-4″), 6.55−6.47 (XX′-part of a AA′XX′-system, 2H, H-3, H-5), 5.18 (s, 1H, NH), 4.68 (d, J = 6.6 Hz, 1H, OCH_2O), 4.63 (d, J = 6.6 Hz, 1H, OCH_2O), 4.62 (m, 1H, H-1′) 3.90 (dd, J = 10.5, 4.0 Hz, 1H, H_a-2′), 3.71 (dd, J = 10.5, 7.6 Hz, 1H, H_b-2′), 3.31 (s, 3H, OCH_3). ^{13}C NMR, HMBC, HSQC (101 MHz, $CDCl_3$): δ = 171.6 (COOH), 151.9 (C4), 139.6 (C1″), 132.2 (2C, C2, C6), 128.9 (2C, C3″, C5″), 127.9 (C4″), 126.8 (2C, C2″, C6″), 117.9 (C1), 112.7 (2C, C3, C5), 96.9 (OCH_2O), 72.4 (C2′), 57.8 (C1′), 55.7 (OCH_3). ESI-MS: m/z (%) = 302.1 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{17}H_{19}NO_4Na]^+$: m/z = 324. 1212, found: 324.1222.

*4-Methoxy-N-[2-(methoxymethoxy)-1-phenylethyl]aniline (**7**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with 4-methoxyaniline (**1e**, 24.6 mg, 0.20 mmol) and DMM (2.5 mL). After 20 h, purification by thin-layer chromatography (cyclohexane/AcOEt/NEt_3 = 90/7/3) afforded the title compound (42.8 mg, 75%) as a yellow oil. The minor regioisomer *N*-(2,2-dimethoxy-1-phenylethyl)-4-methoxyaniline could not be separated (isomeric ratio 4.3:1)

R_f = 0.37(cyclohexane/AcOEt/Et_3N = 7.5/2.0/0.5). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.45−7.39 (m, 2H, H-2″, H-6″), 7.36−7.29 (m, 2H, H-3″, H-5″), 7.28−7.24 (m, 1H, H-4″), 6.77−6.66 (BB′-part of a AA′BB′-system, 2H, H-3, H-5), 6.52−6.47 (AA′-part of a AA′BB′-system, 2H, H-2, H-6), 4.68 (d, J = 6.6 Hz, 1H, OCH_2O), 4.63 (d, J = 6.6 Hz, 1H, OCH_2O), 4.46 (dd, J = 8.3, 4.0 Hz, 1H, H-1′), 3.83 (dd, J = 10.3, 4.0 Hz, 1H, H_a-2′), 3.69 (s, 3H, OCH_3), 3.63 (dd, J = 10.3, 8.3 Hz, 1H, H_b-2′), 3.32 (s, 3H, CH_2OCH_3). ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ = 152.3 (C4), 141.8 (C1), 140.8 (C1″), 128.8 (2C, C3″, C5″), 127.9 (C4″), 127.0 (2C, C2″, C6″), 115.2 (2C, C2, C6), 114.8 (2C, C3, C5), 96.8 (OCH_2O), 72.6 (C2′), 59.2 (C1′), 55.8 (OCH_3), 55.6 (CH_2OCH_3). ESI-MS: m/z (%) = 288.1 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{17}H_{21}NO_3Na]^+$: m/z = 310.1419, found: 310.1415.

*N-[2-(Methoxymethoxy)-1-phenylethyl]-2,4,6-trimethylaniline (**8**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with 2,4,6-trimethylaniline (**1f**, 27.0 mg, 0.20 mmol) and DMM (2.5 mL). After 20 h, purification by thin-layer chromatography (cyclohexane/AcOEt/NEt_3 = 90/7/3) afforded the title compound (46.0 mg, 77%) as a yellow oil. The minor regioisomer *N*-(2,2-dimethoxy-1-phenylethyl)-2,4,6-trimethylaniline could not be separated (isomeric ratio 4.6:1).

R_f = 0.44 (cyclohexane/AcOEt/NEt_3 = 90/7/3). ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ = 7.40−7.23 (m, 5H, Ar-H), 6.77 (s, 2H, H-3, H-5), 4.59 (s, 2H, OCH_2O), 4.30 (pseudo-t, J = 4.9 Hz, 1H, H-1′), 3.9−3.81 (m, 2H, H_a-2′, H_b-2′), 3.20 (s, 3H, OCH_3), 2.20 (s, 3H, C4-CH_3), 2.15 (s, 6H, C2-CH_3, C6-CH_3). ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ = 142.4 (C1), 142.2 (C2″), 129.6 (2C, C3, C5), 128.4 (2C, C3″, C5″), 127.2 (C4″), 127.2 (2C, C2″, C6″), 96.8 (OCH_2O), 70.8 (C2′), 61.4 (C1′), 55.5 (OCH_3), 20.7 (C4-CH3), 18.9 (2C, C2-CH_3, C6-CH_3). Three quaternary carbons could not be dedicated out of the mixture. ESI-MS: m/z (%) = 300.1 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{19}H_{25}NONa]^+$: m/z = 322.1783, found: 322.1787.

*N-[1-(2,4-Dimethoxyphenyl)-2-(methoxymethoxy)ethyl]-4-methylaniline (**9**).* According to the general procedure, 2,4-dimethoxybenzaldehyde (**2b**, 49.9 mg, 0.30 mmol 1.5 equiv) was reacted with *p*-toluidine (**1b**, 21.4 mg, 0.20 mmol) and DMM (2.5 mL). After 20 h, purification by thin-layer chromatography (cyclohexane/AcOEt/NEt_3 = 80/15/5) afforded the title compound (47.0 mg, 71%) as a yellow oil. The minor regioisomer *N*-[1-(2,4-dimethoxyphenyl)-2,2-dimethoxyethyl]-4-methylaniline could not be separated (isomeric ratio 3.5:1).

R_f = 0.35 (cyclohexane/AcOEt/Et_3N = 7.5/2.0/0.5). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.29−7.24 (m, 1H, H-6″), 6.89−6.86 (XX′-part of a AA′XX′-system, 2H, H-3, H-5), 6.48−6.46 (m, 1H, H-3″), 6.46−6.42 (AA′-part of a AA′XX′-system, 2H, H-2, H-6), 6.42−6.48 (m, 1H, H-5″), 4.83 (dd, J = 7.3, 3.9 Hz, 1H, H-1′), 4.66 (d, J = 6.5 Hz, 1H, OCH_2O), 4.60 (d, J = 6.5 Hz, 1H, OCH_2O), 3.89−3.85 (m, 4H, Ar-OCH_3, H_a-2′), 3.77 (s, 3H, Ar-OCH_3), 3.60 (dd, J = 10.2, 7.3 Hz, 1H, H_b-2′), 3.32 (s, 3H, CH_2OCH_3), 2.18 (s, 3H, C4-CH_3). ^{13}C NMR, HMBC, HSQC (101 MHz, $CDCl_3$): δ = 160.1 (CH_3OC_q), 157.9 (CH_3OC_q), 145.4 (C1), 129.6 (2C, C3, C5), 128.5 (C6″), 126.6 (C4) 120.5 (C1″), 113.9 (2C, C2, C6), 104.3 (C5″), 98.7 (C3″), 96.7 (OCH_2O), 70.9 (C2′), 55.5 (CH_2OCH_3), 55.5 (OCH_3), 55.4 (OCH_3), 52.4 (C1′), 20.5 (C4-CH_3). Three carbons at 145.4, 126.6, 120.6 were dedicated out of the HMBC spectrum. ESI-MS: m/z (%) = 332.0 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{19}H_{25}NO_4Na]^+$: m/z = 354.1681, found: 354.1690.

*N-[1-Cyclohexyl-2-(methoxymethoxy)ethyl]-4-methylaniline (**13**).* According to the general procedure, cyclohexanecarbaldehyde (**2e**, 33.7 mg, 0.30 mmol 1.5 equiv) was reacted with *p*-toluidine (**1b**, 21.4 mg, 0.20 mmol) and DMM (2.5 mL). After 20 h reaction time, the crude product was isolated as described and purified by HPLC (ACE 5 C18-PFP, 150 × 30 mm, isocratic: water/acetonitrile for 2 min (90/10), 30 mL/min, then gradient 15 min →100% acetonitrile 30 mL/min, 17.8 min) to afford the title compound (28.85 mg, 52%) as a colorless oil.

R_f = 0.50 (cyclohexane/AcOEt/Et_3N = 7.5/2.0/0.5). IR (ATR): 3400 (w, br), 2923 (s), 2852 (m), 1681 (m), 1520 (s), 1146 (m), 1112 (m), 1045 (s), 807 (m). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 6.99−6.92 (XX′-part of a AA′XX′-system, 2H, H-3, H-5), 6.56−6.50 (AA′-part of a AA′XX′-system, 2H, H-2, H-6), 4.61 (d, J = 6.5 Hz, 1H, OCH_2O), 4.59 (d, J = 6.5 Hz, 1H, OCH_2O), 3.65−3.56 (m, 2H, H_a-2′, H_b-2′), 3.34 (s, 3H, OCH_3), 3.31−3.25 (m, 1H, H-1′), 2.22 (s, 3H, C4-CH_3), 1.95−1.87 (m, 1H, CH_2), 1.81−1.70 (m, 3H, CH_2), 1.70−1.59 (m, 2H, CH_2), 1.31−0.97 (m, 5H, CH_2). ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ = 146.0 (C1), 129.9 (2C, C3, C5) 126.2 (C4), 113.5 (2C, C2, C6), 96.9 (OCH_2O), 67.5 (C2′), 58.1 (C1′), 55.5 (OCH_3), 39.9 (C1″), 30.0, 29.5, 26.7, 26.6, 26.6 (5 × CH_2), 20.5 (C4-CH_3). ESI-MS: m/z (%) = 278.2 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{17}H_{27}NO_2Na]^+$: m/z = 300.1939, found: 300.1947.

*N-[2-(2-Methoxyethoxy)-1-phenylethyl]aniline (**15**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with aniline (**1a**, 18.6 mg, 0.20 mmol) and DME (2.5 mL). After 20 h, the reaction mixture was filtered and washed with DCM (40 mL) and ethyl acetate (40 mL). After 20 h, purification by flash chromatography (cyclohexane/AcOEt/NEt_3 = 90/7/3) afforded the title compound (33.1 mg, 61%) as a colorless oil.

R_f = 0.30 (cyclohexane/AcOEt/Et_3N = 7.0/2.5/0.5). IR (ATR): 3390 (w, br), 3025 (w), 2924 (m, sh), 1733 (w), 1601 (s), 1504 (s), 1104 (s, sh), 751 (s), 701 (s, sh). ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ = 7.44−7.39 (m, 2H, H-2″, H-6″), 7.36−7.29 (m, 2H, H-3″, H-5″), 7.28−7.24 (m, 1H, H-4″), 7.11−7.03 (m, 2H, H-3, H-5), 6.66 (tt, J = 7.3, 1.1 Hz, 1H, H-4), 6.55−6.59 (m, 2H, H-2, H-6), 4.53 (dd, J = 9.0, 4.0 Hz, 1H, H-1′), 3.75 (dd, J = 10.3, 4.0 Hz, 1H, H_a-2′), 3.68 (pseudo-t, J = 4.5 Hz, 1H, H_a-1‴), 3.65−3.61 (m, 1H, H_b-1‴), 3.60−3.52 (m, 3H, CH_2), 3.39 (s, 3H, OCH_3). ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ = 147.9 (C1), 140.8 (C1″), 129.1 (2C, C3, C5), 128.8 (2C, C3″, C5″), 127.5 (C4″), 126.9 (2C, C2″, C6″), 117.7 (C4), 114.1 (2C, C2, C6), 75.9 (C2′), 72.0 (C2‴), 70.3 (C1‴), 59.2 (OCH_3), 58.2 (C1′). ESI-MS: m/z (%) = 272.1 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{17}H_{21}NO_2Na]^+$: m/z = 294.1470 found: 294.1470.

*N-[2-(2-Methoxyethoxy)-1-phenylethyl]-4-methylaniline (**16**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with *p*-toluidine (**1b**, 21.4 mg, 0.20 mmol) and DME (2.5 mL). After 20 h, purification by chromatography (cyclohexane/AcOEt/NEt_3 = 90/7/3) afforded the title compound (36.5 mg, 64%) as a pale yellow oil.

R_f = 0.30 (cyclohexane/AcOEt/Et_3N = 7.5/2.0/0.5). IR (ATR): 3383 (w, br), 2919 (m, sh), 1618 (m), 1520 (s), 1453 (m), 1106 (s, sh), 809 (m), 702 (m). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.44−7.39 (m, 2H, H-2″, H-6″), 7.35−7.29 (m, 2H, H-3″, H-5″), 7.27−7.22 (m, 1H, H-4″), 6.91−6.85 (XX′-part of a AA′XX′-system, 2H, H-3, H-5), 6.47−6.41 (AA′-part of a AA′XX′-system, 2H, H-2, H-6), 4.50 (dd, J = 9.1,

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4.0 Hz, 1H, H-1′), 3.73 (dd, J = 10.3, 4.0 Hz, 1H, H_a-2′), 3.71−3.66 (m, 1H, H_a-1‴), 3.64−3.59 (m, 1H, H_b-1‴), 3.59−3.57 (m, 1H, H_b-2′), 3.56−3.52 (m, 2H, H_a-2‴, H_b-2‴), 3.39 (s, 3H, OCH_3), 2.18 (s, 3H, C4-CH_3). ^{13}C NMR, HMBC, HSQC (101 MHz, $CDCl_3$): δ = 145.5 (C1), 140.8 (C1″), 129.4 (2C, C3, C5), 128.6 (2C, C3″, C5″), 127.3 (C4″), 126.8 (2C, C2″, C6″), 126.7 (C4), 114.1 (2C, C2, C6), 75.8 (C2′), 71.8 (C2‴), 70.1 (C1‴), 59.1 (OCH_3), 58.3 (C1′), 20.4 (C4-CH_3). ESI-MS: m/z (%) = 286.1 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{18}H_{23}NO_2Na]^+$: m/z = 308.1626, found: 308.1637.

*N-[2-(2-Methoxyethoxy)-1-phenylethyl]-2,4,6-trimethylaniline (**17**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with 2,4,6-trimethylaniline (**1f**, 27.0 mg, 0.20 mmol) and DME (2.5 mL). After 20 h, purification by chromatography (cyclohexane/AcOEt/NEt_3 = 90/7/3) afforded the title compound (26.9 mg, 43%) as a yellow oil.

R_f = 0.40 (cyclohexane/AcOEt/Et_3N = 7.5/2.0/0.5). IR (ATR): 3383 (w, br), 2922 (s, sh), 2873 (s), 1734 (m), 1485 (s), 1453 (s), 1109 (s, sh), 734 (m) 700 (s). ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ = 7.39−7.33 (m, 2H, H-2″, H-6″), 7.33−7.27 (m, 2H, H-3″, H-5″), 7.27−7.21 (m, 1H, H-4″), 6.75 (s, 2H, H-3, H-5), 4.27 (t, J = 5.0 Hz, 1H, H-1′), 3.79 (d, J = 5.0 Hz, 2H, H-2′), 3.60−3.55 (m, 2H, H-1‴), 3.52−3.46 (m, 2H, H-2‴), 3.32 (s, 3H, OCH_3), 2.19 (s, 3H, C4-CH_3), 2.14 (s, 6H, C2-CH_3, C6-CH_3). ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ = 142.3 (2C, C1, C1′), 130.8 (C4), 129.6 (2C, C3, C5), 129.5 (2C, C2, C6), 128.3 (2C, C3″, C5″), 127.3 (2C, C2″, C6″), 127.2 (C4″), 74.7 (C2′), 72.0 (C2‴), 70.7 (C1‴), 61.5 (C1′), 59.1 (OCH_3), 20.7 (C4-CH_3), 18.9 (2C, C2-CH_3, C6-CH_3). ESI-MS: m/z (%) = 314.2 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{20}H_{28}NO_2]^+$: m/z = 314.2120, found: 314.2119.

*4-{[2-(2-Methoxyethoxy)-1-phenylethyl]amino}benzoic Acid (**18**).* According to the general procedure, benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) was reacted with 4-aminobenzoic acid (**1d**, 27.4 mg, 0.20 mmol) and DME (2.5 mL). After 20 h, the reaction mixture was filtered and the filter cake was washed with DCM (40 mL) and methanol (40 mL). The combined filtrates were concentrated *in vacuo*, and the resulting crude product was purified by HPLC (ACE 5 C18-PFP, 150 × 30 mm, isocratic: water/acetonitrile (60/40), 30 mL/min, 9.3 min) to afford the title compound (32.8 mg, 52%) as a colorless amorphous solid.

R_f = 0.52 (AcOEt). IR (ATR): 3344 (w, br), 2891 (w, br), 1671 (m), 1604 (s), 1528 (m), 1420 (m), 1283 (m), 1102 (m, sh). ^{1}H NMR, COSY (600 MHz, $CDCl_3$): δ = ^{1}H NMR 7.80 (d, J = 8.4 Hz, 2H, H-2, H-6), 7.38−7.35 (m, 2H, H-2″, H-6″), 7.35−7.31 (m, 2H, H-3″, H-5″), 7.29−7.25 (m, 1H, H-4″), 6.48 (d, J = 8.4 Hz, 2H, H-3, H-5), 5.31 (br s, 1H, NH), 4.61 (dd, J = 8.1, 3.4 Hz, 1H, H-1′), 3.80 (dd, J = 10.4, 3.4 Hz, 1H, H_a-2′), 3.72−3.67 (m, 1H, H_a-1‴) 3.65−3.59 (m, 2H, H_b-2′, H_b-1‴), 3.59−3.53 (m, 2H, H_a-2‴, H_b-2‴), 3.40 (s, 3H, OCH_3). ^{13}C NMR, HMBC, HSQC (151 MHz, $CDCl_3$): δ = 171.5 (COOH), 152.2 (C4), 139.7 (C1″), 132.2 (2C, C2, C6), 129.0 (2C, C3″, C5″), 127.9 (C4″), 126.7 (2C, C2″, C6″), 118.0 (C1), 112.9 (2C, C3, C5), 75.5 (C2′), 72.0 (C2‴), 70.5 (C1‴), 59.2 (OCH_3), 57.7(C1′). Two carbons at 171.5, 118.0 were dedicated out of the HMBC spectrum. ESI-MS: m/z (%) = 316.1 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{18}H_{21}NO_4Na]^+$: m/z = 338.1368, found: 338.1376.

*N-[1-Cyclohexyl-2-(2-methoxyethoxy)ethyl]-4-methylaniline (**19**).* According to the general procedure, cyclohexanecarbaldehyde (**2e**, 33.7 mg, 0.30 mmol 1.5 equiv) was reacted with *p*-toluidine (**1b**, 21.4 mg, 0.20 mmol) and DME (2.5 mL). After 20 h, purification by thin-layer chromatography (cyclohexane/AcOEt/NEt_3 = 7.5/2.0/0.5) afforded the title compound (22.1 mg, 38%) as a colorless oil.

R_f = 0.45 (cyclohexane/AcOEt/Et_3N = 7.5/2.0/0.5). IR (ATR): 3385 (w, br), 2923 (s), 2853 (m), 1618 (m), 1520 (s), 1449 (m) 1251 (m), 1119 (m, sh), 807 (m). ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ = 6.98−6.91 (XX′-part of a AA′XX′-system, 2H, H-3, H-5,), 6.56−6.50 (AA′-part of a AA′XX′-system, 2H, H-2, H-6), 3.60−3.53 (m, 3H, CH_2), 3.53−3.47 (m, 3H, CH_2), 3.37 (s, 3H, OCH_3), 3.27 (pseudo-q, J = 4.9 Hz, 1H, H-1′), 2.22 (s, 3H, C4-CH_3), 1.92−1.82 (m, 1H, CH_2), 1.81−1.69 (m, 3H, CH_2), 1.69−1.58 (m, 2H, CH_2), 1.32−0.93 (m, 5H, CH_2). ^{13}C NMR, HMBC, HSQC (101 MHz, $CDCl_3$): δ = 146.2 (C1), 129.9 (2C, C3, C5), 126.1 (C4), 113.5 (2C, C2, C6), 72.1 (C2″), 70.9 (C2′), 70.7 (C1″), 59.2 (OCH_3), 58.1 (C1′), 39.8 (C1‴), 29.9, 29.4, 26.7, 26.6, 26.6 (5 x CH_2), 20.5 (C4-CH_3). ESI-MS: m/z (%) = 292.2 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{18}H_{29}NO_2Na]^+$: m/z = 314.2096, found: 314.2100.

*2-[(4-Methylphenyl)amino]-2-phenylethanol (**20a**).* TiO_2 (20 mg, 0.25 mmol, 1.3 equiv) and $(NH_4)_2S_2O_8$ (6 mg) were dispersed in a mixture of water (2.5 mL) and DMM (2.5 mL). After the addition of benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) and *p*-toluidine (**1b**, 21.4 mg, 0.20 mmol), the reaction mixture was degassed with argon for 1 min and stirred for 20 h under UV-A (400 W) at room temperature. Then, it was filtered and the filter cake was washed with DCM (40 mL) and ethyl acetate (40 mL). The combined filtrates were concentrated *in vacuo*, and the resulting residue was dissolved in DCM (40 mL) and filtered again. After the removal of DCM, the residue was dissolved in THF (0.2 mL). To the resulting mixture were added water (0.5 mL) and 1 M HCl (4 mL), and the mixture was stirred at 60 °C for 12 h. After cooling to room temperature, water (10 mL) was added and the solution was made alkaline by addition of 1 N NaOH prior to extraction with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (cyclohexane/AcOEt = 4/1) to afford the title compound (21.8 mg, 48%) as a yellow oil).

R_f = 0.21 (cyclohexane/AcOEt/Et_3N = 7.0/2.5/0.5). IR (ATR): 3388 (s, br), 3025 (m), 2920 (m), 2868 (m), 1616 (m), 1517 (s), 1302 (m), 1068 (m), 808 (s), 701 (m). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.39−7.32 (m, 4H, Ar-H), 7.30−7.24 (m, 1H, H-1′), 6.96−6.90 (XX′-part of a AA′XX′-system, 2H, H-3″, H-5″), 6.54−6.49 (AA′-part of a AA′XX′-system, 2H, H-2″, H-6″), 4.49 (dd, J = 7.2, 4.2 Hz, 1H, H-2), 3.93 (dd, J = 11.1, 4.2 Hz, 1H, H_a-1), 3.73 (dd, J = 11.1, 7.2 Hz, 1H, H_b-1), 2.21 (s, 3H, C4″-CH_3). ^{13}C NMR, HMBC, HSQC (101 MHz, $CDCl_3$): δ = 145.0 (C1″), 140.4 (C1′), 129.8 (2C, C3″, C5″), 128.9 (2C, C3′, C5′), 127.7 (C4′), 127.3 (C4″), 126.8 (2C, C2′, C6′), 114.2 (2C, C2″, C6″), 67.5 (C1), 60.3 (C2), 20.5 (C4″-CH_3). ESI-MS: m/z (%) = 228.1 (100) $[M + H]^+$.

The spectroscopic data are in accordance with the literature.[37]

*2-Phenyl-2-(phenylamino)ethanol (**20b**).* TiO_2 (20 mg, 0.25 mmol, 1.3 equiv) and $(NH_4)_2S_2O_8$ (6 mg) were dispersed in a mixture of water (2.5 mL) and DMM (2.5 mL). After the addition of benzaldehyde (**2a**, 31.8 mg, 0.30 mmol 1.5 equiv) and aniline (**1a**, 18.6 mg, 0.20 mmol), the reaction mixture was degassed with argon for 1 min and stirred for 20 h under UV-A (400 W) at room temperature. Then, it was filtered and washed with DCM (40 mL) and ethyl acetate (40 mL). The filtrate was concentrated *in vacuo*, and the resulting residue was dissolved in DCM (40 mL) and filtered again. After the removal of DCM, the residue was dissolved in THF (0.2 mL). To the resulting mixture were added water (0.5 mL) and 1 M HCl (4 mL), and the mixture was stirred at 60 °C for 12 h. After cooling to room temperature, water (10 mL) was added and the solution was made alkaline by addition of 1 N NaOH prior to extraction with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (cyclohexane/AcOEt = 8/2) to afford the title compound (17.9 mg, 42%) as a yellow oil).

R_f = 0.19 (cyclohexane/AcOEt/Et_3N = 7.0/2.5/0.5). IR (ATR): 3520 (m, sh), 3396 (s, br), 1601 (s), 1503 (s), 1316 (m), 1066 (m), 1028 (m), 750 (s), 649 (s). ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ = 7.41−7.31 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.31−7.24 (m, 1H, H-4″), 7.15−7.06 (m, 2H, H-3′, H-5′), 6.68 (tt, J = 7.4, 1.0 Hz, 1H, H-4′), 6.61−6.54 (m, 2H, H-2′, H-6′), 4.52 (dd, J = 6.9, 4.2 Hz, 1H, H-2), 3.96 (dd, J = 11.1, 4.2 Hz, 1H, H_a-1), 3.77 (dd, J = 11.1, 6.9 Hz, 1H, H_b-1). ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ 147.2 (C1′), 140.1 (C1″), 129.3 (2C, C3′, C5′), 129.0 (2C, C3″, C5″), 127.8 (C4″), 126.9 (2C, C2″, C6″), 118.1 (C4′), 114.1 (2C, C2′, C6′), 67.5 (C1), 60.1 (C2). ESI-MS: m/z (%) = 214.0 (100) $[M + H]^+$.

The spectroscopic data are in accordance with the literature.[37]

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■ ASSOCIATED CONTENT

Supporting Information

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One- and two-dimensional NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236−10254.
(2) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212−11222.
(3) Andreatta, J. R.; McKeown, B. A.; Gunnoe, T. B. *J. Organomet. Chem.* **2011**, *696*, 305−315.
(4) Nakao, Y. *Chem. Rec.* **2011**, *11*, 242−251.
(5) Foley, N. A.; Lee, J. P.; Ke, Z.; Gunnoe, T. B.; Cundari, T. R. *Acc. Chem. Res.* **2009**, *42*, 585−597.
(6) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72.
(7) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654−2672.
(8) Ramachary, D. B.; Jain, S. *Org. Biomol. Chem.* **2011**, *9*, 1277−1300.
(9) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442−524.
(10) Brauch, S.; Gabriel, L.; Westermann, B. *Chem. Commun.* **2010**, *46*, 3387−3389.
(11) Essamlali, Y.; Amadine, O.; Maati, H.; Abdelouahdi, K.; Fihri, A.; Zahouily, M.; Varma, R. S.; Solhy, A. *ACS Sustainable Chem. Eng.* **2013**, *1*, 1154−1159.
(12) Azath, I. A.; Puthiaraj, P.; Pitchumani, K. *ACS Sustainable Chem. Eng.* **2013**, *1*, 174−179.
(13) Brahmachari, G.; Banerjee, B. *ACS Sustainable Chem. Eng.* **2014**, *2*, 411−422.
(14) Rossi, B.; Pastori, N.; Prosperini, S.; Punta, C. *Beilstein J. Org. Chem.* **2015**, *11*, 66−73.
(15) Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem.* **2014**, *16*, 2958−2975.
(16) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561−2576.
(17) Lahm, G.; Deichmann, J.-G.; Rauen, A. L.; Opatz, T. *J. Org. Chem.* **2015**, *80*, 2010−2016.
(18) Pastori, N.; Gambarotti, C.; Punta, C. *Mini-Rev. Org. Chem.* **2009**, *6*, 184−195.
(19) Rossi, B.; Prosperini, S.; Pastori, N.; Clerici, A.; Punta, C. *Molecules* **2012**, *17*, 14700.
(20) Clerici, A.; Porta, O. *Tetrahedron Lett.* **1990**, *31*, 2069−2072.
(21) Cannella, R.; Clerici, A.; Pastori, N.; Regolini, E.; Porta, O. *Org. Lett.* **2005**, *7*, 645−648.
(22) Zhang, L.; Deng, Y.; Shi, F. *Tetrahedron Lett.* **2013**, *54*, 5217−5219.
(23) Yamada, K.-i.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509−3511.
(24) Jin, J.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 1565−1569.
(25) Hoffmann, N. *Aust. J. Chem.* **2015**, *68*, 1621−1639.
(26) Tauber, J.; Imbri, D.; Opatz, T. *Molecules* **2014**, *19*, 16190.
(27) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931−1934.
(28) Yadav, J. S.; Reddy, A. R.; Narsaiah, A. V.; Reddy, B. V. S. *J. Mol. Catal. A: Chem.* **2007**, *261*, 207−212.
(29) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326−329.
(30) Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169−1173.
(31) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733−2746.
(32) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431.
(33) Williamson, K. S.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 4570−4571.
(34) Selva, M.; Fabris, M.; Lucchini, V.; Perosa, A.; Noe, M. *Org. Biomol. Chem.* **2010**, *8*, 5187−5198.
(35) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454.
(36) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973−3975.
(37) Mukherjee, A.; Dateer, R. B.; Chaudhuri, R.; Bhunia, S.; Karad, S. N.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 15372−15375.
(38) Kison, C.; Opatz, T. *Eur. J. Org. Chem.* **2008**, *2008*, 2740−2745.
(39) Akindele, T.; Yamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.-i.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5729−5732.
(40) Yamada, K.-i.; Nakano, M.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805−3808.
(41) Clerici, A.; Ghilardi, A.; Pastori, N.; Punta, C.; Porta, O. *Org. Lett.* **2008**, *10*, 5063−5066.
(42) Prosperini, S.; Pastori, N.; Ghilardi, A.; Clerici, A.; Punta, C. *Org. Biomol. Chem.* **2011**, *9*, 3759−3767.
(43) Aldridge, C. L.; Zachry, J. B.; Hunter, E. A. *J. Org. Chem.* **1962**, *27*, 47−51.
(44) Dyker, G. *J. Org. Chem.* **1993**, *58*, 6426−6428.
(45) Ohishi, T.; Yamada, J.; Inui, Y.; Sakaguchi, T.; Yamashita, M. *J. Org. Chem.* **1994**, *59*, 7521−7522.

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