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# Stereoselective Arylation of Amino Aldehydes: Overriding Natural Substrate Control Through Chelation

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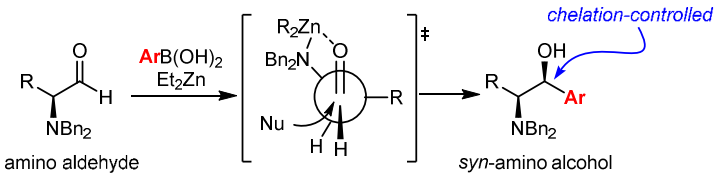
**Abstract.** The chelation-controlled arylation reaction of chiral, enantiopure acyclic α-amino aldehydes enabled by a B/Zn exchange reaction between arylboronic acids and $Et_2Zn$ is reported. The presence of dibenzyl substituents at the nitrogen plays a key role in the stereochemical outcome of the reaction, and chelation is favored over the natural tendency of this type of substrate to undergo Felkin-Anh controlled additions with organomagnesium and organolithium reagents.

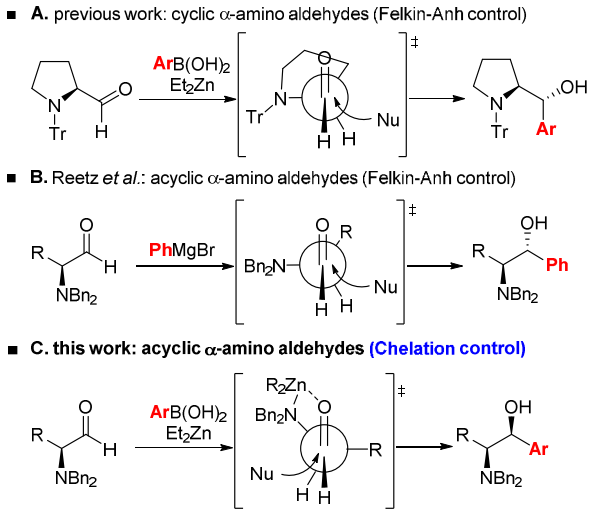
**Keywords:** arylation, chelation control, stereoselective synthesis, amino alcohols, organozinc.

**Graphical Abstract:**



Stereoselective reactions that take advantage of existing stereochemistry in a given molecule to control the generation of new stereocenters are of great importance in organic chemistry, particularly in the synthesis of natural products and biologically relevant molecules.[1] In this context, the substrate-controlled, diastereoselective addition of organometallic reagents to aldehydes and ketones is a fundamental transformation that enables an increase in molecular complexity by carbon-carbon bond formation together with the creation of a new stereogenic center. In this context, the diastereoselective arylation of chiral, non-racemic α-oxygenated aldehydes, readily available from carbohydrates,[2] was enabled by the use of the boron-zinc exchange reaction for the generation of transferable aryl groups.[3,4] The aldehydes underwent smooth arylation in good to excellent diastereoselectivity, and the stereochemistry of the newly formed stereocenter was proposed to be the result of a chelation-controlled process. In further studies from our group, we examine whether our method could be applied to the arylation of chiral *N*-trityl-L-prolinal, and excellent diastereoselectivity was achieved in favor of the Felkin product,[5] contrasting with the results observed using α-oxygenated aldehydes, which underwent chelation-controlled additions (Scheme 1A).[6] The presence of the bulky triphenylmethyl group at the nitrogen had a crucial role, preventing coordination of the zinc atom, therefore avoiding the Cram-chelation transition state. The same behavior was observed by others in the addition of Grignard reagents to *N*-Tr-L-prolinal.[7] Actually, the chelation-controlled addition of organometallic reagents to amino aldehydes and ketones is difficult to attain, and usually the Felkin product has been obtained as the major product.[8] Worth mentioning is the work of Reetz that introduced the *N,N*-dibenzylamino aldehydes as substrates for addition of organometallic reagents with high Felkin selectivity (Scheme 1B).[9,10] Chelation-controlled additions have been observed in a few cases,[11] but usually an excess of a strong Lewis acid,[10] a titanium reagent (*e.g.*, generated from 8 equiv PhMgBr and 10

equiv $Ti(O\textit{i}\text{-}Pr)_4$),[12] or a co-solvent such as $Me_2S$[13] are necessary to attain good selectivities in favor of the chelation-controlled product.



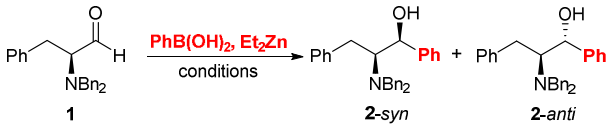

**Scheme 1.** Key precedents in the arylation of amino aldehydes and this work.

As part of our research program focused on the development of efficient and stereoselective arylation methods in organic synthesis, we hypothesized that the combination of Reetz´s *N,N*-dibenzylamino aldehydes and the B/Zn exchange method for the generation of reactive aryl groups would allow us to override the natural tendency of these substrates to undergo addition reactions under Felkin-Anh control. The slightly less bulky *N*-$Bn_2$ substituent, compared to the *N*-Tr group, is expected to play a key role in the stereochemical outcome of the arylation reaction, since we believe that appropriate conditions might be found in which a chelated-transition state might be energetically favored over the Felkin-Anh transition state. Therefore, herein we report the chelation-controlled arylation reaction of enantiopure, acyclic α-amino aldehydes (Scheme 1C).

We started our studies with the phenyl transfer reaction to L-phenylalanine derived amino aldehyde **1**. The reactive transferable phenyl group was generated by the

reaction of phenylboronic acid and diethylzinc. The results of the optimization studies are depicted in Table 1. The first condition tested used toluene as the solvent, and the arylation reaction was performed at room temperature (entry 1). Albeit a modest yield was obtained, we were pleased to find that the **2**-*syn* amino alcohol was formed as the major product, in a 5:1 ratio, as the result of a chelation-controlled process. We further examined the effect of the temperature of the arylation step (entries 2 and 3), and we have found that performing the reaction at 0 $^{o}$C the diastereoselectivity was slightly improved and the desired **2**-*syn* product was formed in a dr of 6:1 (entry 3). Increasing the reaction time from 8 h to 20 h resulted in an increase in the diastereoselectivity (entry 4). In addition, we evaluated the effect of THF and dichloromethane as co-solvents (entries 5 and 6). The use of THF resulted in a reversal of the diastereoselectivity of the reaction, and the **2**-*anti* product was observed as the major diastereoisomer (entry 5). On the other hand, dichloromethane was beneficial for the yield, however, a substantial erosion of the dr was observed (entry 6). Finally, we were pleased to find that performing the reaction in toluene at 0 $^{o}$C, using an excess of the arylating agent, was highly beneficial to the chelation-controlled pathway, and the desired **2**-*syn* product was isolated in 67% yield with an excellent diastereomeric ratio of >20:1 (entry 7).

**Table 1.** Optimization of the reaction conditions[a]




| entry | solvent | temp (°C) | time (h) | yield (%)[b] | *dr syn:anti*[c] |
|---|---|---|---|---|---|
| 1 | toluene | 25 | 4 | 62 | 5:1 |
| 2 | toluene | 60 | 2 | 78 | 4:1 |
| 3 | toluene | 0 | 8 | 61 | 6:1 |
| 4 | toluene | 0 | 20 | 63 | 10:1 |
| 5[d] | toluene/THF | 0 | 8 | 48 | 1:9 |
| 6[d] | toluene/$CH_2Cl_2$ | 0 | 24 | 86 | 3:1 |
| 7[e] | toluene | 0 | 24 | 67 | >20:1 |

[a] Reactions were performed using aldehyde **1** (1.0 equiv, added as a 0.5 M solution in $CH_2Cl_2$) and 2.4 equiv of PhZnEt (generated *in situ* by reaction of $PhB(OH)_2$ (2.4 equiv) and $Et_2Zn$ (1.5 M solution in toluene, 7.2 equiv). [b] Isolated yield. [c] Determined by $^1H$ NMR. [d] 1:1 v/v. [e] 4.0 equiv of PhZnEt were used.

The absolute stereochemistry of the newly generated stereocenter was assigned as being (*S*), by comparison with literature NMR data.[14] The observed absolute configuration corresponds to the chelation-controlled addition product. This behavior is in strong contrast to what was observed in our previous work on the arylation of *N*-Tr-L-prolinal and also in the addition of Grignard reagents to *N*,*N*-dibenzylamino aldehydes, which led to high selectivity favoring the Felkin product. To confirm the stereochemical assignment we have also performed the addition of PhMgBr to **1** and compared the $^1H$ NMR with the product resulting from the arylation under our optimized conditions. As can be seen from the NMR in Figure 1 (bottom), the addition of PhMgBr resulted in a diastereomeric ratio of 10:1 of the **2**-*anti* as a major product, resulting from a Felkin-Anh addition, as described by Reetz.[9] On the other hand, using our arylation method a

single product can be observed in the NMR spectrum (Figure 1, top), corresponding to **2**-*syn*, which is the minor diastereomer observed in the Grignard addition.

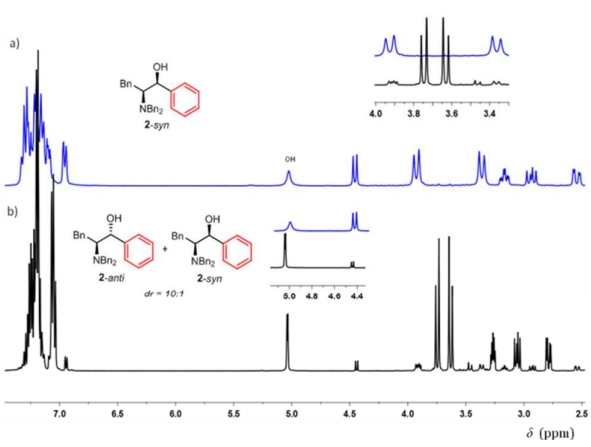
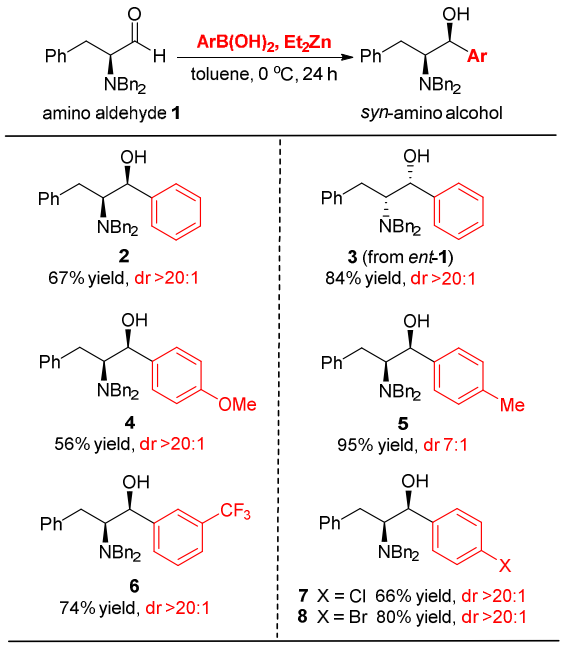



**Figure 1.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra for a) **2**-*syn*, obtained by arylation of 1 with $PhB(OH)_2/Et_2Zn$, and b) **2**-*syn* + **2**-*anti* (dr = 10:1), obtained by arylation of **1** with PhMgBr.

With the success of the chelation-controlled phenyl transfer reaction to amino aldehyde **1**, we investigated the arylation reaction with a broader range of arylboronic acids (Table 2). The presence of substituents with different electronic effects at the aryl group, such as *p*-OMe (**4**), *m*-$CF_3$ (**6**), *p*-Cl (**7**), and *p*-Br (**8**) was well tolerated, and the products have been obtained in excellent diastereoselectivities. An exception to this behavior was observed with the *p*-Me (**5**) substituted boronic acid, which led to the corresponding product in lower selectivity (dr = 7:1). As expected, both enantiomers of the *syn* amino alcohols (**2** and **3**) can be efficiently prepared through our method, by starting either with the D or L enantiomer of phenylalanine.

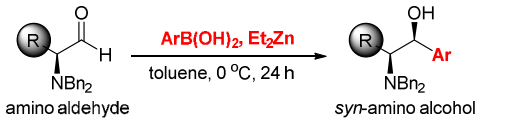
**Table 2.** Scope of the arylation for amino aldehyde **1**[a]




[a]Isolated yields. Diastereomeric ratios determined by $^1$H NMR analysis of the crude product.

Further studies to expand the scope with respect to the side chain of the α-amino aldehyde have been carried out. The arylation reaction works efficiently with a number of different amino aldehydes derived from L-leucine, L-valine, L-*iso*-leucine, L-serine, L-alanine, D-alanine, L-phenylglycine and D-phenylglycine (Table 3). For aldehydes bearing an alkyl side chain the corresponding *syn*-amino alcohols were obtained in good yields and excellent diastereoselectivity (products **9**-**11** and **13**-**16**, 58-92% yield, dr >20:1). The method allows the synthesis of an enantiopure amino alcohol with three contiguous stereocenters (product **11**, 77% yield, dr >20:1) and the L-serine-derived aldehyde leads to *syn*-amino alcohol bearing an additional protected hydroxy group that can be used for further elaboration (product **12**, 70% yield, dr >20:1).

**Table 3.** Scope of the arylation reaction[a]

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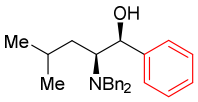
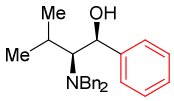
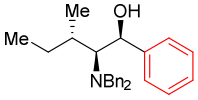
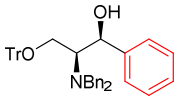
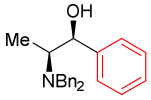
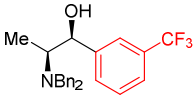
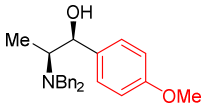
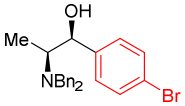
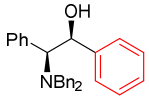
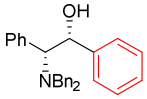
|---|---|
|  **9** 92% yield, dr >20:1 |  **10** 83% yield, dr >20:1 |
|  **11** 77% yield, dr >20:1 |  **12** 70% yield, dr >20:1 |
|  **13** 73% yield, dr >20:1 |  **14** 60% yield, dr >20:1 |
|  **15** 62% yield, dr >20:1 |  **16** 58% yield, dr >20:1 |
|  **17** 65% yield, dr >20:1 |  **18** 82% yield, dr >20:1 |

[a] Isolated yields. Diastereomeric ratios determined by $^1$H NMR analysis of the crude product.

Worth pointing out is that products **13** (from L-alanine) and **17**-**18** (from both enantiomers of phenylglycine) have the core structure of pseudoephedrine and pseudoephenamine (Figure 2), which are the chiral source of well known chiral auxiliaries which have found use in Myers´ asymmetric alkylation of enolates,[15] aldol reactions,[16] conjugate additions,[15c] Claisen rearrangements,[17] α-arylation of amino acids,[18] and epoxidation of enones.[19]

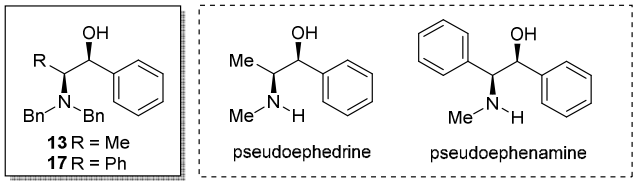
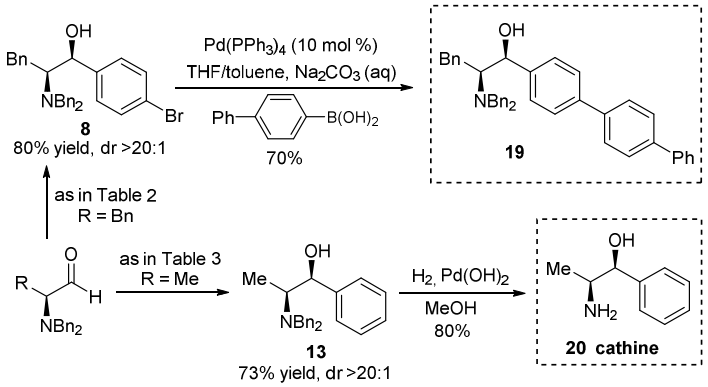



**Figure 2.** Comparison of the structures of compounds **13** and **17** with chiral auxiliaries pseudoephedrine and pseudoephenamine.

Despite the advantages of the efficient synthesis of arylated amino alcohols, the present method is not without its limitations. The reaction is sensitive to steric hindrance in the arylating agent. For example, when 2-methoxyphenyl- and 2,4,6-trimethylphenylboronic acids were used as precursors of the arylating agent, no arylation product was formed, and the transfer of the ethyl group was observed instead (57-60% yield, dr >20:1). The use of sterically less demanding groups led to a mixture of aryl and ethyl addition products (Ar = 1-naphthyl: 55% yield, Ar *vs* Et transfer 1:3; Ar = 4-biphenyl: 60% yield, Ar *vs* Et transfer 1:1). In these examples both the aryl and ethyl transfer were obtained in excellent diastereoselectivities through a chelation-controlled addition. These results observed with bulkier aryl groups might suggest that the mechanism goes through an intramolecular delivery of the nucleophile, in the zinc-chelated pre-transition state. When the aryl group becomes bulkier, steric encumbering in the transition state arrangement increases the energy for the arylation pathway, and the transfer of the less sterically demanding ethyl group becomes energetically favored.

To highlight the utility of the reaction developed, we synthesized two biologically relevant molecules using the diastereoselective arylation as the key step (Scheme 2). L-Phenylalanine-derived amino alcohol **8**, which was obtained in 80% yield and excellent diastereoselectivity, was further elaborated into the terphenyl derivative **19** through a Pd-catalyzed Suzuki cross-coupling reaction with biphenylboronic acid. The resulting compound is structurally related to terphenylalanine derivatives that have found use as

fluorescent probes for protein monitoring.[20] Similarly, amino alcohol **13** (obtained from L-alaninal in 73% yield; dr >20:1) displays the core structure and stereochemistry of the psychostimulant natural alkaloid cathine (norpseudoephedrine) **20**, isolated from *Catha edulis*.[21] We therefore accomplished a straightforward total synthesis of cathine through removal of the both *N*-benzyl groups of **13** through hydrogenolysis under $Pd(OH)_2$ catalysis in 80% yield.




**Scheme 2.** Utility of the diastereoselective arylation for the synthesis of biologically relevant molecules.

In summary, we have developed an efficient method for the synthesis of enantiopure *syn* β-amino alcohols, through a highly diastereoselective arylation of *N,N*-dibenzylamino aldehydes. The stereochemistry of the newly installed stereocenter is proposed to be the result of a chelation-controlled addition, enabled by the *in situ* generation of reactive aryl-zinc-ethyl reagents through a B/Zn exchange reaction. This reactive arylating agent allowed us to override the natural tendency of these types of α-amino aldehydes to undergo Felkin-Anh controlled additions of organometallic reagents. The method developed is therefore complementary to addition of Grignard reagents and should find its place in the toolbox of synthetic organic chemists for the synthesis of valuable chiral compounds.

## Experimental Section

**General Information**. Air- and moisture-sensitive reactions were conducted in flame- or oven-dried glassware equipped with tightly fitted rubber septa and under a positive pressure of dry argon. Reagents and solvents were handled by using standard syringe techniques. Flash column chromatography was performed using silica gel (230-400 mesh) or neutral alumina (70-290 mesh). Thin layer chromatography (TLC) was performed using supported silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or treated with acidic vanillin followed by heating. NMR spectra were recorded either in a 300, 400, or 500 MHz instrument in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of residual $CHCl_3$ or tetramethylsilane (TMS) as reference. The data are reported as follows: chemical shift (δ), multiplicity, coupling constant (*J*) in Hz, and integrated intensity. $^{13}C$ NMR spectra were recorded at 75, 100, and 125 MHz in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak $CDCl_3$. Abbreviations to denote the multiplicity of a particular signal are: s (singlet), d (doublet), t (triplet), dd (double doublet), m (multiplet), q (quartet), quint (quintet), and br (broad singlet). ESI-QTOF-MS measurements were performed in the positive ion mode (*m/z* 50-2000 range). IR spectra were obtained on an FTIR-ATR instrument. Melting points were recorded using an optical microscope apparatus and are uncorrected. Optical rotations were measured using a polarimeter and are reported as $[\alpha]_D^{20}$, unless otherwise noted.

**Procedure for the Arylation of *N,N*-dibenzylamino Aldehydes.** Under an argon atmosphere, a 1.5 mol $L^{-1}$ solution of $Et_2Zn$ (12.0 equiv, 3.6 mmol, 2.4 mL) was slowly added to a solution of arylboronic acid (4.0 equiv, 1.2 mmol) in dry toluene (3 mL). The mixture was stirred at 60 ºC for 1 h and, after this period, cooled to 0 ºC and a solution of the aldehyde[22] (1.0 equiv, 0.3 mmol) in 1 mL of dry dichloromethane was

added. The reaction was stirred at 0 ºC for 24 h and then 5 mL of water were added carefully at 0 ºC. The product was extracted with ethyl acetate (3 x 10 mL) and washed with NaCl/$NH_4Cl$ (2:1 w/w) solution. The combined extracts were dried with $MgSO_4$ and evaporated. The residue was purified by flash chromatography in neutral alumina, typically eluting with a mixture of hexane/EtOAc, 85:15.

*Note: The quality of the boronic acid is crucial for achieving best results. We recommended recrystallization of the boronic acid before using in the B/Zn exchange reaction.*

**(1*S*,2*S*)-2-(dibenzylamino)-1,3-diphenylpropan-1-ol** (**2**). White solid, 67% yield (0.082 g, 0.20 mmol). Mp: 110-113 ºC. $[\alpha]_D^{20}$ = +90.9 (c 0.274, DCM). IR ($\nu$ $cm^{-1}$): 702, 727, 754, 1013, 1030, 1056, 1073, 1406, 1453, 1492, 2857, 2926, 3030, 3246. $^1$H NMR (300 MHz, $CDCl_3$) δ: 2.54 (dd, *J* = 14.6, 3.5 Hz, 1H), 2.93 (dd, *J* = 14.6, 9.4 Hz, 1H), 3.13-3.20 (m, 1H), 3.36 (d, *J* = 13.5 Hz, 2H), 3.92 (d, *J* = 13.5 Hz, 2H), 4.45 (d, *J* = 9.4 Hz, 1H), 5.02 (br, 1H), 6.94-7.32 (m, 20H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 32.2, 53.7, 65.9, 73.7, 126.0, 127.2, 127.7, 127.71, 128.2, 128.3, 128.4, 129.1, 138.5, 140.1, 141.9. HRMS (ESI) *m/z*: calc. for $[C_{29}H_{29}NO+H]^+$ = 408.2327, found 408.2344.

**(1*R*,2*R*)-2-(dibenzylamino)-1,3-diphenylpropan-1-ol** (**3**). White solid, 84% yield (0.102 g, 0.25 mmol). Mp: 110-113 ºC. $[\alpha]_D^{20}$ = -93.4 (c 0.491, DCM). IR ($\nu$ $cm^{-1}$): 702, 732, 753, 1012, 1030, 1056, 1073, 1406, 1457, 1496, 2857, 2926, 3030, 3250. $^1$H NMR (300 MHz, $CDCl_3$) δ: 2.54 (dd, *J* = 14.6, 3.5 Hz, 1H), 2.93 (dd, *J* = 14.6, 9.4 Hz, 1H), 3.13-3.20 (m, 1H), 3.36 (d, *J* = 13.5 Hz, 2H), 3.92 (d, *J* = 13.5 Hz, 2H), 4.45 (d, *J* = 9.4 Hz, 1H), 5.02 (br, 1H), 6.94-7.32 (m, 20H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 32.2, 53.7, 65.9, 73.7, 126.0, 127.2, 127.7, 127.71, 128.2, 128.3, 128.4, 129.1, 138.5, 140.1, 141.9. HRMS (ESI) *m/z*: calc. for $[C_{29}H_{29}NO+H]^+$ = 408.2327, found 408.2352.

**(1*S*,2*S*)-2-(dibenzylamino)-1-(4-methoxyphenyl)-3-phenylpropan-1-ol** (**4**). White solid, 56% yield (0.073 g, 0.17 mmol). Mp: 111-114 ºC. $[\alpha]_D^{20}$ = +111.1 (c 0.031, DCM).

IR ($\nu$ $cm^{-1}$): 702, 740, 835, 1034, 1177, 1250, 1457, 1518, 2849, 2935, 3030, 3358. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ: 2.52 (dd, *J* = 14.6, 3.5 Hz, 1H), 2.92 (dd, *J* = 14.6, 9.4 Hz, 1H), 3.10-3.18 (m, 1H), 3.36 (d, *J* = 12.9 Hz, 2H), 3.74 (s, 3H), 3.92 (d, *J* = 12.9 Hz, 2H), 4.42 (d, *J* = 9.4 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 2H), 6.95-7.00 (m, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 7.14-7.33 (m, 13 H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 32.3, 53.7, 55.1, 66.0, 73.2, 113.6, 126.0, 127.2, 128.3, 128.4, 128.7, 129.1, 134.0, 138.6, 140.3, 159.1. HRMS (ESI) *m/z*: calc. for $[C_{30}H_{31}NO_2+H]^+$ = 438.2433, found 438.2420.

**(1*S*,2*S*)-2-(dibenzylamino)-3-phenyl-1-(*p*-tolyl)propan-1-ol** (**5**). Mixture of diastereoisomers (data listed for the major isomer). Colorless oil, 95% yield (0.120 g, 0.28 mmol). $[\alpha]_D^{20}$ = +95.5 (c 0.260, DCM). IR ($\nu$ $cm^{-1}$): 702, 736, 740, 823, 1012, 1026, 1056, 1073, 1457, 1497, 2853, 2922, 3030, 3060, 3319. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H), 2.54 (dd, *J* = 14.5, 3.1 Hz, 1H), 2.90 (dd, *J* = 14.5, 9.0 Hz, 1H), 3.13-3.18 (m, 1H), 3.36 (d, *J* = 12.9 Hz, 2H), 3.91 (d, *J* = 12.9 Hz, 2H), 4.42 (d, *J* = 9.4 Hz, 1H), 4.95 (br, 1H), 6.95-7.30 (m, 20H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 21.1, 32.4, 53.8, 66.0, 73.5, 126.0, 127.2, 127.6, 128.0, 128.3, 128.4, 128.9, 129.2 (2), 137.2, 138.6, 140.3. HMRS (ESI) *m/z*: calc. for $[C_{30}H_{31}NO+H]^+$ = 422.2484, found 422.2488.

**(1*S*,2*S*)-2-(dibenzylamino)-3-phenyl-1-(3-(trifluoromethyl)phenyl)propan-1-ol** (**6**). Colorless oil, 74% yield (0.105 g, 0.22 mmol). $[\alpha]_D^{20}$ = +77.7 (c 0.399, DCM). IR ($\nu$ $cm^{-1}$): 697, 736, 749, 805, 909, 1073, 1120, 1164, 1323, 1453, 1496, 2853, 2926, 3030, 3065, 3194. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ: 2.54 (dd, *J* = 14.1, 4.7 Hz, 1H), 3.04 (dd, *J* = 14.1, 8.2 Hz, 1H), 3.11-3.19 (m, 1H), 3.39 (d, *J* = 12.9 Hz, 2H), 3.96 (d, *J* = 12.9 Hz, 2H), 4.49 (d, *J* = 9.4 Hz, 1H), 5.09 (br, 1H), 6.90 (d, *J* = 6.4 Hz, 2H), 7.12-7.42 (m, 17H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 32.1, 53.8, 65.6, 73.3, 124.0 (q, $^{1}J$ = 203 Hz), 124.5 (q, $^{3}J$ = 2.8 Hz), 124.7 (q, $^{3}J$ = 2.8 Hz), 126.1, 127.4, 128.4, 128.5, 128.6, 129.0, 129.2, 130.4 (q, $^{2}J$ = 24 Hz), 130.8, 138.4, 139.4, 143.2. HRMS (ESI) *m/z*: calc. for $[C_{30}H_{28}F_3NO+H]^+$ = 476.2201, found 476.2231.

**(1*S*,2*S*)-1-(4-chlorophenyl)-2-(dibenzylamino)-3-phenylpropan-1-ol** (**7**). White solid, 66% yield (0.087 g, 0.20 mmol). Mp: 100-103 ºC. $[\alpha]_D^{20}$ = +111.0 (c 0.323, DCM). IR (ν $cm^{-1}$): 697, 736, 753, 836, 1017, 1052, 1397, 1458, 1497, 2365, 2840, 2862, 3030, 3065, 3233. $^1$H NMR (500 MHz, $CDCl_3$) δ: 2.52 (dd, *J* = 14.7, 4.4 Hz, 1H), 2.96 (d, *J* = 14.7, 8.8 Hz, 1H), 3.07-3.12 (m, 1H), 3.37 (d, *J* = 13.2 Hz, 2H), 3.92 (d, *J* = 13.2 Hz, 2H), 4.41 (d, *J* = 9.3 Hz, 1H), 5.00 (br, 1H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 7.14-7.32 (m, 15H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 32.2, 53.8, 65.8, 73.0, 126.1, 127.3, 128.3, 128.4, 128.45, 129.0, 129.1, 129.15, 138.4, 139.8, 140.6. HRMS (ESI) *m/z*: calc. for $[C_{29}H_{28}ClNO+H]^+$ = 442.1938, found 442.1951.

**(1*S*,2*S*)-1-(4-bromophenyl)-2-(dibenzylamino)-3-phenylpropan-1-ol** (**8**). White solid, 80% yield (0.117 g, 0.24 mmol). Mp: 106-109 ºC. $[\alpha]_D^{20}$ = +103.8 (c 0.456, DCM). IR (ν $cm^{-1}$): 702, 740, 835, 1012, 1056, 1073, 1393, 1458, 1497, 2853, 2922, 3030, 3285. $^1$H NMR (300 MHz, $CDCl_3$) δ: 2.50 (dd, *J* = 14.6, 4.1 Hz, 1H), 2.93 (dd, *J* = 14.6, 8.8 Hz, 1H), 3.03-3.11 (m, 1H), 3.34 (d, *J* = 13.5 Hz, 2H), 3.90 (d, *J* = 13.5 Hz, 2H), 4.38 (d, *J* = 9.4 Hz, 1H), 5.02 (br, 1H), 6.88-6.94 (m, 4H), 7.12-7.30 (m, 15H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 32.0, 53.6, 65.6, 73.0, 121.3, 126.0, 127.2, 128.2, 128.3, 129.0 (2), 129.2, 131.1, 138.3, 141.1. HRMS (ESI) *m/z*: calc. for $[C_{29}H_{28}BrNO+H]^+$ = 486.1432, found 486.1433.

**(1*S*,2*S*)-2-(dibenzylamino)-4-methyl-1-phenylpentan-1-ol** (**9**). White solid, 92% yield (0.103 g, 0.28 mmol). Mp: 93-96 ºC. $[\alpha]_D^{20}$ = +92.1 (c 0.518, DCM). IR (ν $cm^{-1}$): 702, 736, 745, 1030, 1453, 2853, 2926, 2957, 3030, 3060, 3389. $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.57 (d, *J* = 6.4 Hz, 3H), 0.64 (d, *J* = 6.4 Hz, 3H), 0.68-0.79 (m, 1H), 1.09-1.18 (m, 1H), 1.46-1.55 (m, 1H), 2.72-2.79 (m, 1H), 3.45 (d, *J* = 13.5 Hz, 2H), 3.94 (d, *J* = 13.5 Hz, 2H), 4.36 (d, *J* = 9.4 Hz, 1H), 7.09-7.35 (m, 15H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 22.4, 22.9, 25.4, 35.3, 53.5, 62.2, 74.7, 127.2, 127.4, 127.6, 128.0, 128.4, 129.1, 138.9, 142.1. HRMS (ESI) *m/z*: calc. for $[C_{26}H_{31}NO+H]^+$ = 374.2484, found 374.2485.

**(1*S*,2*S*)-2-(dibenzylamino)-3-methyl-1-phenylbutan-1-ol** (**10**). Colorless oil, 83% yield (0.089 g, 0.25 mmol). $[\alpha]_D^{20}$ = +75.0 (c 0.657, DCM). IR ($\nu$ $cm^{-1}$): 701, 749, 982, 1025, 1073, 1099, 1453, 1492, 2926, 2961, 3030, 3060, 3371. $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.59 (d, *J* = 7.3 Hz, 3H), 0.98 (d, *J* = 7.3 Hz, 3H), 2.04-2.13 (m, 1H), 2.82 (dd, *J* = 9.8, 2.4 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 2H), 4.04 (d, *J* = 13.2 Hz, 2H), 4.67 (d, *J* = 9.8 Hz, 1H), 5.17 (br, 1H), 7.05-7.09 (m, 2H), 7.17-7.22 (m, 3H), 7.24-7.38 (m, 10H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 20.0, 22.8, 25.8, 54.1, 67.0, 70.5, 127.3, 127.6, 128.0, 128.1, 128.5, 129.3, 138.8, 143.0. HRMS (ESI) *m/z*: calc. for $[C_{25}H_{29}NO+H]^+$ = 360.2327, found 360.2314.

**(1*S*,2*S*,3*S*)-2-(dibenzylamino)-3-methyl-1-phenylpentan-1-ol** (**11**). White solid, 77% yield (0.086 g, 0.23 mmol). Mp: 97-100 ºC. $[\alpha]_D^{20}$ = +97.2 (c 0.780, DCM). IR ($\nu$ $cm^{-1}$): 702, 736, 744, 762, 1462, 2360, 2978, 3030, 3294. $^1$H NMR (500 MHz, $CDCl_3$) δ: 0.51-0.59 (m, 1H), 0.67 (t, *J* = 6.8 Hz, 3H), 0.72-0.78 (m, 1H), 1.04 (d, *J* = 7.3 Hz, 3H), 1.80-1.85 (m, 1H), 2.89 (d, *J* = 9.8 Hz, 1H), 3.49 (d, *J* = 13.2 Hz, 2H), 4.04 (d, *J* = 13.2 Hz, 2H), 4.74 (d, *J* = 9.8 Hz, 1H), 5.27 (br, 1H), 7.09-7.11 (m, 2H), 7.18-7.23 (m, 3H), 7.27-7.30 (m, 2H), 7.32-7.37 (m, 8H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 12.6, 16.9, 29.5, 32.1, 53.8, 66.1, 69.8, 127.3, 127.6, 128.0 (2), 128.5, 129.2, 138.8, 142.7. HRMS (ESI) *m/z*: calc. for $[C_{26}H_{31}NO+H]^+$ = 374.2484, found 374.2459.

**(1*S*,2*S*)-2-(dibenzylamino)-1-phenyl-3-(trityloxy)propan-1-ol** (**12**). Pale-yellow solid, 70% yield (0.124 g, 0.21 mmol). Mp: 121-124 ºC. $[\alpha]_D^{20}$ = +50.6 (c 0.634, DCM). IR ($\nu$ $cm^{-1}$): 702, 753, 1025, 1069, 1449, 1492, 2853, 2926, 3026, 3060, 3398. $^1$H NMR (400 MHz, $CDCl_3$) δ: 3.10-3.15 (m, 1H), 3.20-3.29 (m, 2H), 3.40 (d, *J* = 13.2 Hz, 2H), 3.87 (d, *J* = 13.2 Hz, 2H), 4.39 (d, *J* = 10.0 Hz, 1H), 4.95 (br, 1H), 7.00-7.03 (m, 2H), 7.20-7.36 (m, 27H), 7.41-7.52 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 54.4, 59.0, 64.5, 70.6, 87.2, 126.9, 127.1, 127.2, 127.4, 127.7, 127.8, 127.9, 128.2, 128.4, 128.6, 129.1, 138.9,

141.8, 143.4, 146.8. HRMS (ESI) *m/z*: calc. for $[C_{42}H_{39}NO_2+H]^+$ = 590.3059, found 590.3055.

**(1*S*,2*S*)-2-(dibenzylamino)-1-phenylpropan-1-ol** (**13**). Colorless oil, 73% yield (0.072 g, 0.22 mmol). $[\alpha]_D^{20}$ = +128.0 (0.543, DCM). IR ($\nu$ $cm^{-1}$): 702, 736, 749, 805, 1025, 1043, 1142, 1453, 1492, 2840, 2931, 2970, 3030, 3065, 3371. $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.84 (d, *J* = 6.4 Hz, 3H), 2.71-2.81 (m, 1H), 3.34 (d, *J* = 13.5 Hz, 2H), 3.92 (d, *J* = 13.5 Hz, 2H), 4.38 (d, *J* = 9.9 Hz, 1H), 5.03 (br, 1H), 7.10-7.14 (m, 2H), 7.19-7.37 (m, 13H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 7.7, 53.3, 60.1, 74.3, 127.2, 127.3, 127.5, 128.0, 128.5, 129.0, 138.6, 142.0. HRMS (ESI) *m/z*: calc. for $[C_{23}H_{25}NO+H]^+$ = 332.2014, found 332.2014.

**(1*S*,2*S*)-2-(dibenzylamino)-1-(3-(trifluoromethyl)phenyl)propan-1-ol** (**14**). Colorless oil, 60% yield (0.072 g, 0.18 mmol). $[\alpha]_D^{20}$ = +98.5 (c 0.441, DCM). IR ($\nu$ $cm^{-1}$): 670, 700, 734, 752, 803, 1071, 1123, 1166, 1330, 1455, 1493, 2848, 2930, 2968, 3033, 3064, 3361. $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.88 (d, *J* = 6.8 Hz, 3H), 2.69-2.76 (m, 1H), 3.37 (d, *J* = 13.2 Hz, 2H), 3.93 (d, *J* = 13.2 Hz, 2H), 4.41 (d, *J* = 9.6 Hz, 1H), 7.27-7.38 (m, 13H), 7.46-7.48 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 7.8, 53.4, 60.2, 74.0, 124.1(q, $^1J$ = 203 Hz), 124.2 (q, $^3J$ = 2.8 Hz), 124.4 (q, $^3J$ = 2.8 Hz), 127.4, 128.6, 129.1, 130.54, 130.53, 130.47 (q, $^2J$ = 24 Hz), 138.4, 143.3. HRMS (ESI) *m/z*: calc. for $[C_{24}H_{24}F_3NO+H]^+$ = 400.1888, found 400.1889.

**(1*S*,2*S*)-2-(dibenzylamino)-1-(4-methoxyphenyl)propan-1-ol** (**15**). White solid, 62% yield (0.067 g, 0.19 mmol). Mp: 78-80 ºC. $[\alpha]_D^{20}$ = +131.3 (c 0.298, DCM). IR ($\nu$ $cm^{-1}$): 702, 740, 758, 822, 831, 1025, 1143, 1241, 1302, 1380, 1410, 1453, 1514, 1587, 1613, 2836, 2940, 2966, 3030, 3060, 3260. $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.83 (d, *J* = 7.0 Hz, 3H), 2.69-2.79 (m, 1H), 3.34 (d, *J* = 13.5 Hz, 2H), 3.73 (s, 3H), 3.92 (d, *J* = 13.5 Hz, 2H), 4.34 (d, *J* = 9.9 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.23-7.36 (m, 10H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 7.7, 53.3, 55.1, 60.1, 73.8, 113.5, 127.2, 128.3,

128.5, 129.0, 138.7, 159.0. HRMS (ESI) *m/z*: calc. for $[C_{24}H_{27}NO_2+H]^+$ = 362.2120, found 362.2119.

**(1*S*,2*S*)-1-(4-bromophenyl)-2-(dibenzylamino)propan-1-ol** (**16**). White solid, 58% yield (0.071 g, 0.17 mmol). Mp: 118-120 ºC. $[\alpha]_D^{20}$ = +117.7 (c 0.253, DCM). IR ($\nu$ $cm^{-1}$): 702, 736, 753, 818, 1013, 1047, 1069, 1138, 1393, 1453, 1492, 2849, 2922, 3030, 3385. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 0.85 (d, *J* = 7.0 Hz, 3H), 2.63-2.73 (m, 1H), 3.34 (d, *J* = 13.5 Hz, 2H), 3.91 (d, *J* = 13.5 Hz, 2H), 4.33 (d, *J* = 9.9 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.29-7.43 (m, 12H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 7.7, 53.3, 60.1, 73.8, 127.4, 128.5, 128.9, 129.0, 131.2, 138.5, 141.2. HRMS (ESI) *m/z*: calc. for $[C_{23}H_{24}BrNO+H]^+$ = 410.1119, found 410.1120.

**(1*S*,2*S*)-2-(dibenzylamino)-1,2-diphenylethan-1-ol** (**17**). White solid, 65% yield (0.077 g, 0.19 mmol). Mp: 150-152 ºC. $[\alpha]_D^{20}$ = +113.7 (c 0.194, DCM). IR ($\nu$ $cm^{-1}$): 702, 745, 756, 1021, 1051, 1078, 1458, 1497, 2853, 2926, 3030, 3065, 3289. $^1H$ NMR (500 MHz, $CDCl_3$) δ: 3.08 (d, *J* = 13.2 Hz, 2H), 3.77 (d, *J* = 10.7 Hz, 1H), 4.06 (d, *J* = 13.2 Hz, 2H), 5.19 (d, *J* = 10.5 Hz, 1H), 5.20 (br, 1H), 6.98-7.04 (m, 5H), 7.13-7.15 (m, 2H), 7.25-7.39 (m, 13H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: 53.5, 69.1, 70.9, 127.1, 127.3, 127.7, 127.8, 128.0, 128.6, 129.0, 130.2, 132.9, 138.4, 141.3. HRMS (ESI) *m/z*: calc. for $[C_{28}H_{27}NO+H]^+$ = 394.2171, found 394.2172.

**(1*R*,2*R*)-2-(dibenzylamino)-1,2-diphenylethan-1-ol** (**18**). White solid, 82% yield (0.097 g, 0.25 mmol). Mp: 149-151 ºC. $[\alpha]_D^{20}$ = -108.1 (c 0.586, DCM). IR ($\nu$ $cm^{-1}$): 701, 744, 756, 1025, 1051, 1073, 1453, 1492, 2849, 2922, 3030, 3060, 3393. $^1H$ NMR (500 MHz, $CDCl_3$) δ: 3.08 (d, *J* = 13.2 Hz, 2H), 3.77 (d, *J* = 10.7 Hz, 1H), 4.06 (d, *J* = 13.2 Hz, 2H), 5.19 (d, *J* = 10.5 Hz, 1H), 6.98-7.04 (m, 5H), 7.13-7.15 (m, 2H), 7.25-7.39 (m, 13H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: 53.5, 69.1, 70.9, 127.1, 127.3, 127.7, 127.8, 128.0, 128.6, 129.0, 130.2, 132.9, 138.4, 141.3. HRMS (ESI) *m/z*: calc. for $[C_{28}H_{27}NO+H]^+$ = 394.2171, found 394.2161.

**Procedure for the Suzuki-Miyaura Cross-Coupling.** To 6 mL of 1:1 toluene-THF containing **8** (1 equiv, 0.15 mmol, 0.073 g) and 0.063 g (0.32 mmol; 2.12 equiv) of 4-biphenylboronic acid was added a solution of 0.32 mmol (2.12 equiv, 0.034 g) of $Na_2CO_3$ in 2.5 mL of water. The mixture was degassed by bubbling argon through for 30 min, then 0.017 g (10 mol%) of $Pd(PPh_3)_4$ was added. The reaction mixture was stirred vigorously at 80 ºC for 24 h and then 15 mL of water were added. The product was extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried with $MgSO_4$ and evaporated. The Suzuki adduct **19** was purified by flash chromatography in neutral alumina eluting with a mixture of hexane/EtOAc (90:10).

**(1*S*,2*S*)-1-([1,1':4',1''-terphenyl]-4-yl)-2-(dibenzylamino)-3-phenylpropan-1-ol** (**19**). White solid, 70% yield (0.059 g, 0.10 mmol). Mp: 198-201 ºC. $[\alpha]_D^{20}$ = +120.0 (c 0.299, DCM). IR ($\nu$ $cm^{-1}$): 702, 749, 762, 767, 828, 1259, 1276, 2360, 2849, 2992, 3030, 3324. $^1$H NMR (400 MHz, $CDCl_3$) δ: 2.61 (dd, *J* = 14.5, 3.5 Hz, 1H), 3.00 (dd, *J* = 14.5, 8.6 Hz, 1H), 3.21-3.26 (m, 1H), 3.40 (d, *J* = 13.3 Hz, 2H), 3.96 (d, *J* = 13.3 Hz, 2H), 4.53 (d, *J* = 9.8 Hz, 1H), 7.01 (d, *J* = 7.0 Hz, 2H), 7.18-7.39 (m, 16H), 7.45-7.51 (m, 4H), 7.63-7.69 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 32.4, 53.8, 66.0, 73.5, 126.0, 126.8, 127.0, 127.3, 127.32, 127.4, 128.2, 128.3, 128.4, 128.8, 129.2, 138.6, 139.8, 139.9, 140.0, 140.1, 140.6, 141.1. HRMS (ESI) *m/z*: calc. for $[C_{41}H_{37}NO+H]^+$ = 560.2953, found 560.2958.

**Procedure for the Hydrogenolysis of 13: Synthesis of cathine.** A round bottom flask, equipped with a stir bar was charged with **13** (0.072 g, 0.22 mmol), $Pd(OH)_2$ on carbon (20 w%, 0.030 g), and MeOH (2 mL). The flask was purged with hydrogen (1 atm, balloon) for 10 min, then the mixture was stirred vigorously (under hydrogen atmosphere) at room temperature for 48 h. The reaction mixture was dissolved in ethyl acetate (10 mL) and filtered through a pad of Celite. The solvent was removed under reduced pressure to give **20** in an analytically pure form.

**(1*S*,2*S*)-2-amino-1-phenylpropan-1-ol** (**20**). White solid, 80% yield (0.026 g, 0.176 mmol). Mp: 70-72 ºC. $[\alpha]_D^{20}$ = +47.6 (c 0.065, EtOH). IR ($\nu$ $cm^{-1}$): 697, 749, 831, 865, 978, 1025, 1047, 1090, 1449, 1583, 2844, 2862, 2931, 2970, 3035, 3065, 3155, 3289, 3354, 3415. $^1$H NMR (400 MHz, $CDCl_3$) δ: 1.01 (d, *J* = 6.4 Hz, 3H), 2.34 (br, 3H), 3.02 (quint, *J* = 6.4 Hz, 1H), 4.24 (d, *J* = 6.8 Hz, 1H), 7.25-7.34 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 20.5, 52.9, 78.6, 126.5, 127.5, 128.3, 142.6. HRMS (ESI) *m/z*: calc. for $[C_9H_{13}NO+H_2]^{++}$ = 153.1154, found 153.1150.

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**Supporting Information:**

The Supporting Information is available free of charge on the ACS Publications website. Copies of NMR spectra for all compounds.

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