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ARTICLE

Employing carboxylic acids in aryne multicomponent coupling triggered by aziridines/azetidines[†]

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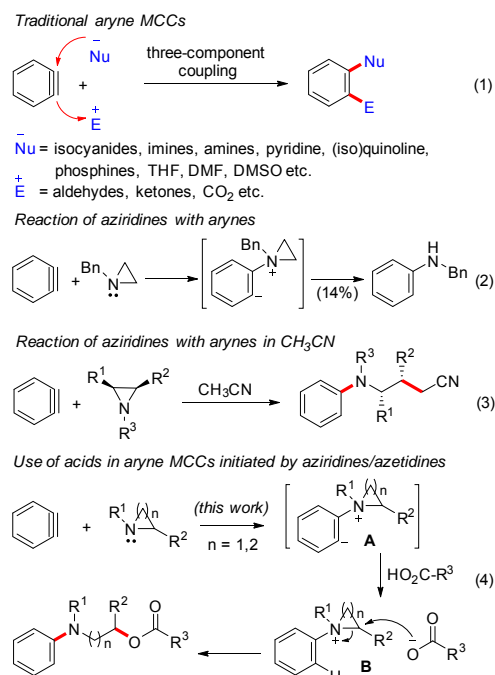
The transition-metal-free aryne multicomponent coupling (MCC) involving carboxylic acids initiated by aziridines/azetidines has been reported. The use of aziridines as nucleophile afforded *N*-aryl β -amino alcohol derivatives and the application of azetidines as nucleophilic trigger furnished *N*-aryl γ -amino alcohol derivatives in moderate to good yields. These reactions proceed under mild conditions and result in the formation of a new carbon-nitrogen bond and a new carbon-oxygen bond. The utility of carboxylic acids in aryne MCCs have been demonstrated, and the synthetic potential of phenols as acid surrogates in the present aryne MCCs has been realized.

Introduction

Among the various methods to build molecular complexity, the multicomponent couplings (MCCs) offer high levels of brevity and diversity, and are routinely used in medicinal and combinatorial chemistry.^{1,2} Engaging arynes in MCCs is one of the transition-metal-free protocols for the rapid access to complex 1,2-disubstituted benzene derivatives.^{3,4} Usually in aryne MCCs, a nucleophile (having no acidic protons) adds to aryne generating the aryl anion intermediate, which is trapped by suitable electrophile (Scheme 1, eq 1).⁵ The commonly used nucleophiles are isocyanides,⁶ imines,⁷ amines,⁸ N-heterocycles⁹ such as pyridine, (iso)quinoline, phosphines,¹⁰ and solvents such as THF,^{6d} DMF¹¹ and DMSO.¹² The electrophilic coupling partner usually used are aldehydes and ketones (including CO₂),^{6a,13} activated imines and electron-deficient alkynes. Intriguingly, the utility of carboxylic acids as a third-component in aryne MCCs, to the best of our knowledge is rare.¹⁴ Moreover, despite the utility of N-heterocycles in aryne MCCs, the use of aziridines as the nucleophilic trigger is limited.

The generation of a zwitterion from aryne and *N*-benzyl aziridine and its subsequent rearrangement to *N*-benzyl aniline in 14% yield was known as early as 1972 (eq 2).^{15a} Moreover, Cu-catalyzed aryne MCCs involving alkenyl aziridines and alkynes have been reported by Pineschi and co-workers.¹⁶ Recently, Larionov and co-workers disclosed the aryne MCCs

initiated by aziridines, where the solvent CH₃CN has been incorporated as the third-component resulting in the synthesis of *N*-aryl γ -aminobutyronitriles (eq 3).^{17a} Very recently, we have developed the trifluoroacetic acid promoted aryne MCC involving arynes, aziridines and water for the synthesis of *N*-aryl β -aminoalcohols derivatives.^{17b} Herein, we report the aryne MCCs initiated by aziridines/azetidines, using carboxylic acids as the third-components.¹⁸ The reaction furnished either *N*-aryl β -amino alcohol derivatives or *N*-aryl γ -amino alcohol derivatives in moderate to good yields under mild conditions.



Scheme 1. Aryne MCCs and use of aziridines as nucleophilic trigger

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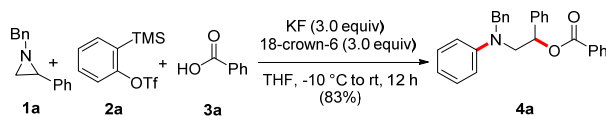
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[†]Electronic Supplementary Information (ESI) available: Details on experimental procedures, characterization data of all compounds, and single crystal X-ray data of compound **4s**. CCDC-1050176. See DOI: 10.1039/x0xx00000x

Mechanistically, the reaction of aziridines with arynes generates the zwitterionic intermediate **A**,^{15a} which is sufficiently basic to deprotonate the carboxylic acid to form the quaternary ammonium salt **B** and the carboxylate anion. Nucleophilic attack of the carboxylate anion on salt **B** affords the *N*-aryl β -amino alcohol derivatives (eq 4). A new carbon-nitrogen bond as well as new carbon-oxygen bond is formed in this reaction. In addition to the use carboxylic acids as third-components, the utility of phenols as third-component in this aryne MCC has been demonstrated.

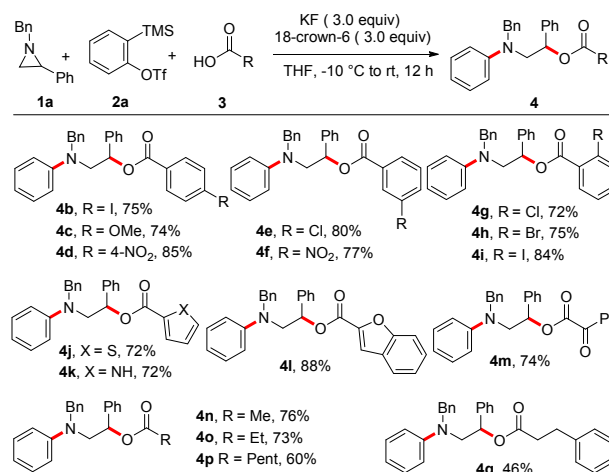
Results and Discussion

The present study was commenced by treating *N*-benzyl aziridine **1a** and benzoic acid **3a** with the aryne generated in situ from 2-(trimethylsilyl)aryl triflate **2a**¹⁹ using KF in presence of 18-crown-6. Using these conditions, a smooth reaction occurred leading to the formation of 2-(benzyl(phenyl)amino)-1-phenylethyl benzoate **4a** in 83% yield (Scheme 2).²⁰ Two-fold excess of KF and 18-crown-6 (relative to **2a**) was needed for good conversion. Notably, the product derived from the rearrangement of the initially formed zwitterion (**A**) from **1a** and aryne was not observed.^{15a} Moreover, the fluorine incorporated product in the reaction of arynes with aziridines recently reported by Wu and Sha was not observed under the optimized conditions.²¹ As the benzoic acid and **2a** were used in slight excess, the insertion product (phenyl benzoate) was observed in ~10% yield under the present conditions.^{14,22}



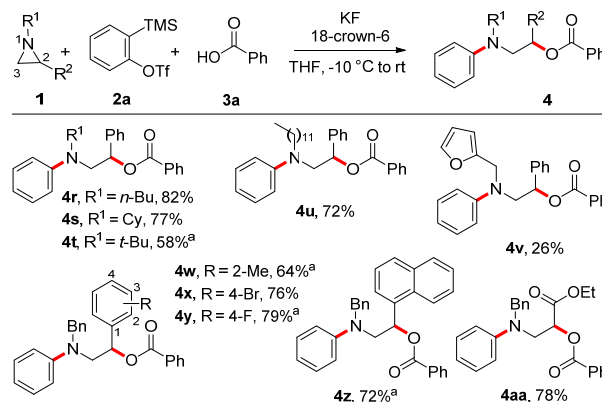
Scheme 2. MCC involving *N*-benzyl aziridine, aryne and benzoic acid

After establishing the protocol for incorporating carboxylic acids in aryne MCCs, we then evaluated the scope of this reaction. First, the effect of various carboxylic acids was examined (Scheme 3). Gratifyingly, benzoic acids having electronically different substituents at the *para*-position of the ring were well-tolerated leading to the synthesis of corresponding *N*-aryl β -amino alcohol derivatives in good yields irrespective of the substrate electronics (**4b-4d**). Moreover, benzoic acids with substituents at the *meta*- and *ortho*-positions of the ring underwent smooth MCCs affording the desired product in high yields (**4e-4i**). Additionally, heteroaromatic carboxylic acids and an α -keto acid could be employed as the third-component furnishing the expected MCC product in good yields (**4j-4m**). Furthermore, MCCs using a series of aliphatic acids resulted in the formation of the target products (**4n-4q**) in moderate to good yields demonstrating the versatility of the present reaction. Notably, stronger acids such as trifluoroacetic acid and trifluoromethanesulfonic acid did not afford the MCC product under the optimized conditions.^{17b}



Scheme 3. Scope of carboxylic acids in aryne MCCs triggered by Aziridines: General conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), **3** (0.75 mmol) KF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (2.0 mL), -10 °C to rt, 12 h. Yields of the isolated products are given.

Next, the scope of this MCC with substituted aziridines was examined (Scheme 4). Interestingly, linear, branched and even sterically demanding substituent on aziridine nitrogen was tolerated (**4r-4v**). The corresponding products were isolated in moderate to good yields. In the case of **4s**, structure was confirmed by single-crystal X-ray analysis.²³ Moreover, aziridines with substitution at the 2-aryl ring underwent efficient MCC under the optimized conditions to afford *N*-aryl β -aryl functionalized β -amino alcohol derivatives **4w-4z** in 64-79% yield. In addition, electron deficient ethyl 1-benzylaziridine-2-carboxylate afforded the desired product **4aa** in 78% yield, thus expanding the scope of this MCC.



Scheme 4. Variation of the aziridine moiety. General conditions: **1** (0.50 mmol), **2a** (0.75 mmol), **3a** (0.75 mmol) KF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (2.0 mL), -10 °C to rt, 12 h. Yields of the isolated products are given. ^a Reaction was performed on 0.25 mmol scale.

The scope of this reaction with differently substituted arynes was also studied (Scheme 5). Electronically different symmetrical 4,5-disubstituted arynes generated from their precursors underwent efficient MCCs with aziridine **1a** and benzoic acid to afford functionalized aromatic amines in good

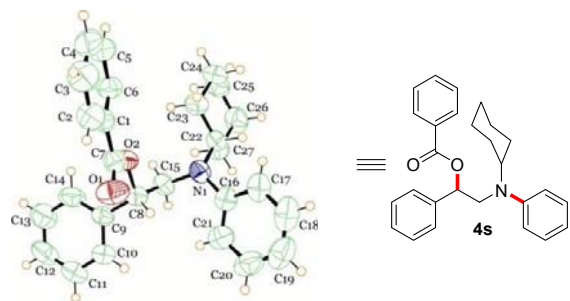
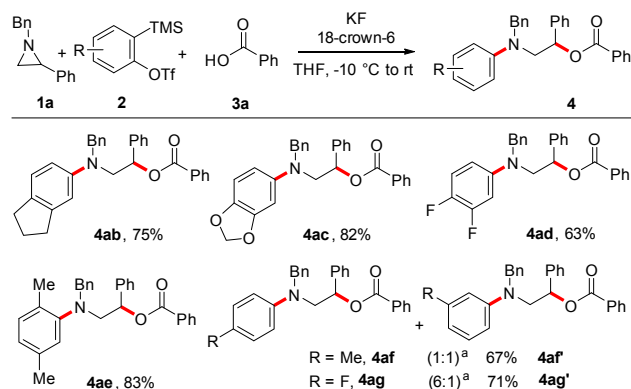


Figure 1. Crystal structure of **4s** (thermal ellipsoids are shown with 50% probability).

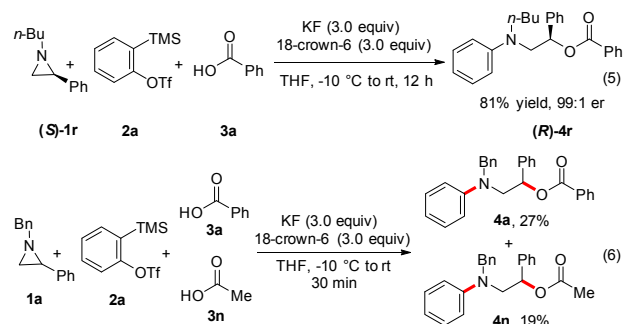
yields (**4ab-4ad**). In addition, the 3,6-dimethyl arylene generated from its precursor afforded the desired product **4ae** in 83% yield. As expected, the 4-methyl benzyne furnished inseparable mixture of regioisomers **4af** and **4af'** in a 1:1 ratio and in 67% yield. Furthermore, an inseparable mixture of regioisomers **4ag** and **4ag'** in a 6:1 ratio and in 71% yield was obtained by using 4-fluorobenzyne as the aryne component in this reaction.



Scheme 5. Variation of the aryne moiety. General conditions: **1a** (0.50 mmol), **2** (0.75 mmol), **3a** (0.75 mmol) KF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (2.0 mL), -10 °C to rt, 12 h. Yields of the isolated products are given. ^a Regioisomer ratio was determined by ¹H NMR analysis of the crude reaction mixture.

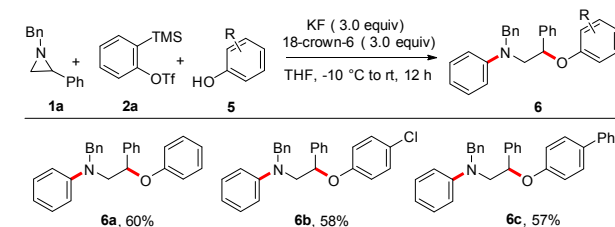
Further experiments have shed light on the mechanism of this transformation. The reaction of enantiomerically pure aziridine (**S**)-**1r** with **2a** and **3a** under the optimized conditions afforded the chiral amino alcohol derivative (**R**)-**4r** in 81% yield and 99:1 er (Scheme 6, eq 5). The formation of (**R**)-**4r** in high er rules out the possibility of S_N1 opening of intermediate **B** (eq 4). The enantiomerically pure (**S**)-**1r** was prepared by the reaction of commercially available (*R*) phenyloxirane with *n*-butylamine followed by the cyclization of the intermediate β-aminoalcohol derivative.²⁴ Moreover, competition experiment carried out using **1a** and aryne generated from **2a** with aromatic acid **3a** and aliphatic acid **3n** revealed that **3a** reacted ~1.5 times faster than **3n** when the reaction was quenched after 30 minutes under the optimized conditions (eq 6). Similar result was obtained when the reaction was quenched after 60 minutes.²⁰ These results tend to indicate that the aromatic

acid being more strong can protonate the aryl anion intermediate **A** (eq 4) faster than the aliphatic acid.



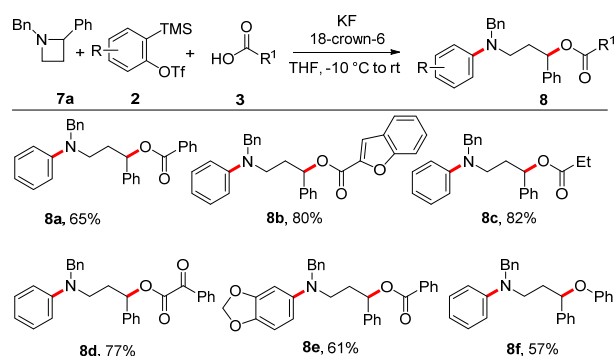
Scheme 6. Mechanistic experiments

Encouraged by the success of the efficient aryne MCCs using carboxylic acids as the third-component, we continued our studies using phenols as the acid surrogate in the present MCC. In a pilot experiment, treatment of **1a** with aryne generated from **2a** and phenol **5a** under optimized reaction conditions resulted in the synthesis of *N*-benzyl-*N*-(2-phenoxy-2-phenylethyl)aniline **6a** in 60% yield (Scheme 7). In this case, the aziridine-aryne adduct **A** (eq 3) was protonated by phenol followed by the nucleophilic attack by the phenoxide ion resulted in the formation of **6**.²⁵ As in the case of reaction with acids, the *O*-arylated phenol was also observed in ~15% yield.¹⁴ The reaction worked reasonably well with 4-Cl and 4-Ph substituted phenols, and the desired products were isolated in moderate yields.



Scheme 7. MCCs Involving Arynes, Phenols and Aziridines. General conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), **5** (0.75 mmol) KF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (2.0 mL), -10 °C to rt, 12 h. Yields of the isolated products are given.

It was found that the present aryne MCCs are not limited to *N*-substituted aziridines as the nucleophilic trigger, but instead *N*-substituted azetidines afforded the corresponding *N*-aryl γ-amino alcohol derivatives in good yields (Scheme 8). The reaction worked well with aromatic, heteroaromatic and aliphatic carboxylic acids and in all cases, the desired product was formed in good yields (**8a-8c**). In addition, α-ketoacid and 4,5-disubstituted symmetrical aryne generated from the precursor also underwent smooth aryne MCCs under the present conditions using azetidine as the nucleophilic trigger (**8d-8e**). In addition, phenol was also used as the acid surrogate in this reaction leading to the formation of the phenoxy derivative **8f** in 57% yield.



Scheme 8. MCCs Involving Arynes, Acids and Azetidines. General conditions: **7a** (0.50 mmol), **2** (0.75 mmol), **3** (0.75 mmol), KF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (2.0 mL), -10 °C to rt, 12 h. Yields of the isolated products are given.

Conclusions

In conclusion, we have developed a practical and efficient MCC involving aryne, aziridines/azetidines and carboxylic acids. The reaction resulted in a transition-metal-free route to *N*-aryl β -amino alcohol derivatives and *N*-aryl γ -amino alcohol derivatives in good yields. The utility of carboxylic acids in aryne MCCs has been demonstrated and phenols can also be used as the acid surrogates in this reaction. Given the importance of amino alcohol derivatives in biological systems, the MCC approach presented herein is likely a method to access these compounds under mild conditions.

Experimental section

General Procedure for the MCC Involving Aziridine, Aryne and Carboxylic Acids: To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) inside a glove box. Carboxylic acid **3** (0.75 mmol) was added outside the glove box under argon atmosphere. The mixture was dissolved in THF (2.0 mL) under argon atmosphere and continued stirring for five minutes at 30 °C. After five minutes of stirring, aziridine **1** (0.5 mmol) was added. Then the reaction mixture was cooled to -10 °C and kept stirring for five minutes. To the stirring solution, aryne precursor **2** (0.75 mmol) was added. Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. After 12 h the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 98/02) on silica gel to afford the corresponding *N*-aryl β -amino alcohol derivatives **4** in moderate to good yields.

2-(Benzyl(phenyl)amino)-1-phenylethyl benzoate (4a). Colorless oil (0.170 g, 83%). R_f (Pet. ether /EtOAc = 95/05): 0.53; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.03 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.48-7.34 (m, 7H), 7.28-7.18 (m, 5H), 7.15 (d, J = 7.2 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.75 (t, J = 7.2 Hz, 1H),

6.39-6.36 (m, 1H), 4.62 (d, J = 17.2 Hz, 1H), 4.35 (d, J = 17.3 Hz, 1H), 4.15 (dd, J_1 = 8.1 Hz, J_2 = 15.4 Hz, 1H), 3.78 (dd, J_1 = 5.2 Hz, J_2 = 15.3 Hz, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.9, 148.4, 138.9, 138.4, 133.1, 130.2, 129.8, 129.4, 128.8, 128.7, 128.5, 128.5, 126.9, 126.7, 126.6, 117.1, 112.8, 74.6, 56.8, 54.7. **HRMS (ESI)** calculated $[\text{M}+\text{H}]^+$ for $\text{C}_{28}\text{H}_{26}\text{O}_2\text{N}$: 408.1958, found: 408.1957. **FTIR** (cm^{-1}) 3022, 2929, 2358, 1718, 1598, 1503, 1451, 1359, 1311, 1268, 1217, 1108, 995, 767.

General Procedure for the MCC Involving Aziridine, Aryne and Phenols: To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) inside a glove box. Phenol **5** (0.75 mmol) was added outside the glove box under argon atmosphere. The mixture was dissolved in THF (2.0 mL) under argon atmosphere and continued stirring for five minutes at 30 °C. After five minutes of stirring, aziridine **1** (0.5 mmol) was added. Then the reaction mixture was cooled to -10 °C and kept stirring for five minutes. To the stirring solution aryne precursor **2** (0.75 mmol) was added. Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. After 12 h the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 98/02) on silica gel to afford the corresponding *N*-aryl β -amino alcohol derivatives **6** in moderate to good yields.

***N*-Benzyl-*N*-(2-phenoxy-2-phenylethyl)aniline (6a).** White solid (0.114 g, 60%). R_f (Pet. ether /EtOAc = 95/05): 0.55; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.48 (d, J = 7.4 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.36-7.18 (m, 10H), 6.91 (t, J = 7.3 Hz, 1H), 6.86-6.83 (m, 4H), 6.77 (t, J = 7.2 Hz, 1H), 5.56 (dd, J_1 = 3.8, J_2 = 8.1 Hz, 1H), 4.83 (d, J = 17.4 Hz, 1H), 4.55 (d, J = 17.4 Hz, 1H), 4.01 (dd, J_1 = 8.2, J_2 = 15.5 Hz, 1H), 3.85 (dd, J_1 = 3.8, J_2 = 15.5 Hz, 1H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 158.0, 148.2, 139.9, 138.8, 129.5, 129.4, 129.0, 128.7, 128.1, 126.8, 126.6, 126.1, 121.0, 116.7, 116.0, 112.4, 78.7, 58.7, 55.1. **HRMS (ESI)** calculated $[\text{M}+\text{H}]^+$ for $\text{C}_{27}\text{H}_{26}\text{ON}$: 380.2009, found: 380.2007. **FTIR** (cm^{-1}) 3020, 2924, 2358, 1596, 1497, 1451, 1358, 1223, 1036, 958, 763, 697.

General Procedure for the MCC Involving Azetidine, Aryne and Carboxylic Acids/Phenol: To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the KF (87 mg, 1.5 mmol) and 18-crown-6 (396 mg, 1.5 mmol) inside a glove box. Carboxylic acid/Phenol **3/5** (0.75 mmol) was added outside the glove box under argon atmosphere. The mixture was dissolved in THF (2.0 mL) under argon atmosphere and continued stirring for five minutes at 30 °C. After five minutes of stirring, azetidine **7** (0.5 mmol) was added. Then the reaction mixture was cooled to -10 °C and kept stirring for five minutes. To the stirring solution, aryne precursor **2** (0.75 mmol) was added. Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. After 12 h the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 98/02) on silica gel to afford the corresponding *N*-aryl γ -amino alcohol derivatives **8** in moderate to good yields.

3-(Benzyl(phenyl)amino)-1-phenylpropyl benzoate (8a). White solid (0.137 g, 65%). R_f (Pet. ether /EtOAc = 95/05): 0.40; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.13 (d, $J = 7.5$ Hz, 2H), 7.61 (t, $J = 7.3$ Hz, 1H), 7.51–7.45 (m, 4H), 7.40 (t, $J = 7.4$ Hz, 2H), 7.36–7.30 (m, 3H), 7.27–7.19 (m, 5H), 6.73 (t, $J = 8.0$ Hz, 3H), 6.09 (dd, $J_1 = 7.9$ Hz, $J_2 = 5.3$ Hz, 1H), 4.56 (q, $J = 16.9$ Hz, 2H), 3.71–3.46 (m, 2H), 2.49–2.42 (m, 1H), 2.38–2.30 (m, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.9, 148.3, 140.3, 138.9, 133.2, 130.3, 129.8, 129.4, 128.7, 128.7, 128.6, 128.3, 127.0, 126.8, 126.4, 116.7, 112.6, 74.9, 54.8, 47.5, 33.8. HRMS (ESI) calculated $[\text{M}+\text{H}]^+$ for $\text{C}_{29}\text{H}_{28}\text{NO}_2$: 422.2115, found: 422.2119. FTIR (cm^{-1}) 3022, 2974, 2403, 1716, 1599, 1505, 1443, 1363, 1269, 1217, 1111, 926, 773.

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