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Organocatalysis

Amine Functionalization through Sequential Quinone-Catalyzed Oxidation/Nucleophilic Addition

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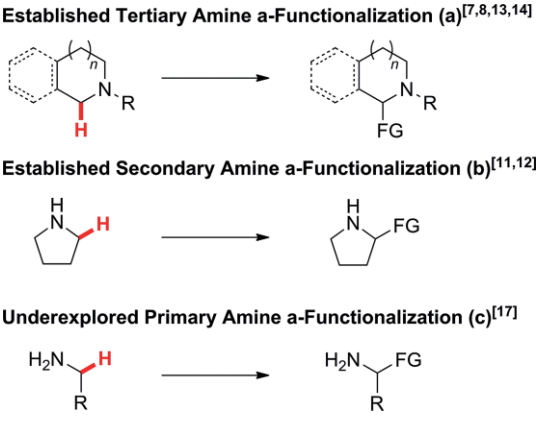
Abstract: A simple and efficient method for the synthesis of α-branched amines through formal oxidative C–H functionalization is reported. A commercially available quinone organocatalyst is employed to promote the aerobic oxidation of primary amines to the corresponding N-protected imines, which are then trapped in situ with an appropriate nucleophile to give access to versatile functionalized amines in good to excellent yields (70–90 %).

Introduction

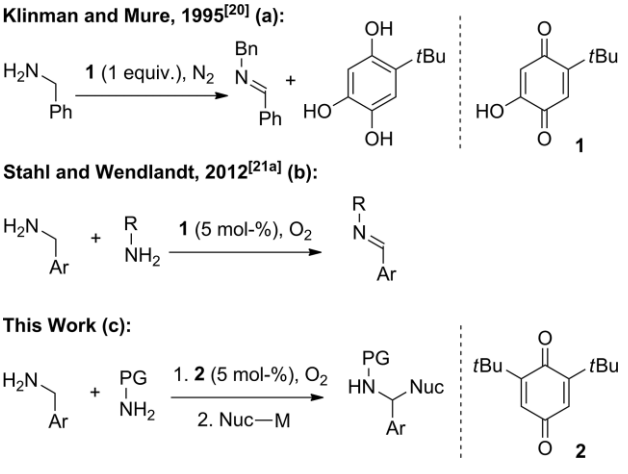
The importance of amines in many disciplines of chemistry has fueled the development of a variety of methods to enable their synthesis, including amine alkylation,[1] reductive amination,[2] and imine addition.[3] More recently, hydroamination[4,5] and C–H amination[6] methods have been reported. These powerful methods for the synthesis of amine are conceptually related in that they deliver the target amine by means of C–N bond construction. In comparison, there are only few methods that enable the direct α-functionalization of amine-containing molecules.

MacMillan,[7] Stephenson,[8] and others[9] have utilized photoredox catalysis to enable a variety of amine C–H α-functionalizations, but these reactions are currently limited to applications involving tertiary amine substrates (Scheme 1 a).[10] Krische has demonstrated that transfer hydrogenation can be used to functionalize secondary amines (Scheme 1 b).[11] Stoichiometric methods that enable the functionalization of secondary[12] and tertiary[13,14] amines have also been reported. Dehydrogenative cross-coupling has also been heavily utilized to enable the functionalization of such substrates.[15,16] On the other hand, the α-functionalization of primary amines has been underexplored (Scheme 1 c).[17] To address this gap, we have developed a new protocol that enables the formal α-functionalization of primary amines through sequential quinone-catalyzed amine oxidation/nucleophilic addition.

In biology, quinone cofactors are commonly employed by copper amine oxidases to enable the conversion of primary amines to the corresponding aldehyde derivatives.[18] Corey and Achiwa were the first to show that quinones could be used to promote the stoichiometric oxidation of an amine to the corresponding ketone in an abiotic environment.[19] Later studies by Klinman and Mure further demonstrated that appropriate



Scheme 1. Established amine α-functionalizations and the underexplored α-functionalization of primary amines. FG = functional group; EWG = electron-withdrawing group.



Scheme 2. Key precedents and present application to formal amine α-functionalization. PG = protecting group.

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cofactor analogs could be utilized to enable the oxidation of benzylic amines to provide dimeric imines (Scheme 2 a).[20] The potential synthetic utility of cofactor mimics of this type has recently been recognized and this has led to the development of new organocatalytic protocols for amine oxidation by Stahl (Scheme 2 b)[21] and others.[22–24]

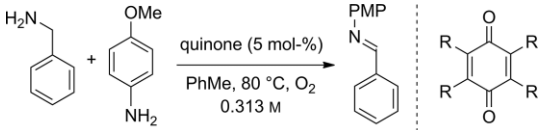
Results and Discussion

We sought to explore the possibility of using sequential quinone-catalyzed amine oxidation/nucleophilic addition to enable the formal oxidative functionalization of amine substrates (Scheme 2 c). In such a process, we envisioned that quinone-catalyzed amine oxidation would deliver an N-protected imine intermediate (not shown) that could be trapped in situ by an appropriate nucleophilic reaction partner (Nuc–M) to deliver the desired amine product. Herein, we report the development of this method and its application to the efficient synthesis of α-branched amines.

Using Wendlandt and Stahl's protocol as a starting point,[21a] we set out to identify a commercially available alternative to quinone **1**[25] that would enable catalytic amine oxidation (Table 1). It was found that 1,4-benzoquinone (**5**) and methyl 1,4-benzoquinone (**6**) provided very poor conversion to the desired *N*-*para*-methoxyphenyl (PMP) imine (**4a**, 0 and 44 % yield, respectively). When examining 2,5-substitution patterns on the quinone catalyst, we found that none of the commercial quinones were superior to quinone **1**, which facilitated amine oxidation in near quantitative yield. Tetrasubstituted quinones gave universally poor conversion. Duroquinone (**11**) and tetrahydroxy-1,4-benzo-quinone (**12**) failed to provide the desired imine product. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, **13**) provided imine **4a** in only 28 % yield. Finally, 2,6-disubstituted quinones were studied and commercially available quinone **2** was identified as a suitable catalyst, providing the desired oxidation product in initially 80 % yield. Increasing the reaction concentration while employing quinone **2** as the catalyst provided imine **4a** in a satisfactory yield of 97 %. Important trends can be inferred from analysis of these data. Quinones that are prone to 1,4-addition (**5** and **6**)[26] or addition/elimination processes (**10**, **14**, and **15**) are ineffective catalysts. Additionally, very sterically encumbered (**7** and **11**) and electron-rich quinones (**8** and **12**) that likely fail to undergo amine condensation are generally ineffective. DDQ (**13**) also provides poor conversion, perhaps owing to its inability to undergo oxidative turnover under these conditions. Taken together, these studies have led us to conclude that to promote amine oxidation, a quinone catalyst must 1) be sterically encumbered or electronically constituted in such a way as to prevent conjugate addition of the amine, 2) be sterically accessible to allow condensation of an amine substrate, and 3) provide a reduced catalyst that is sufficiently electron rich to undergo catalytic turnover by autoxidation.[20b] Quinone **2** meets all of these criteria and, therefore, serves as an efficient catalyst for amine oxidation.

With the optimized conditions for amine oxidation in hand, sequential oxidation/nucleophilic addition reactions were examined. These studies began by exploring the efficiency of in situ addition reactions by using the lithiated ketene imine derived from acetonitrile[27] as the nucleophilic reaction partner in combination with a variety of imines generated through quinone-promoted amine oxidation to deliver a series of β-amino nitriles (**17**, Table 2). A wide range of benzylic amines

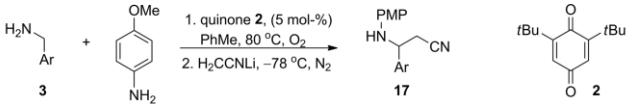
Table 1. Optimization of the amine oxidation protocol.[a]

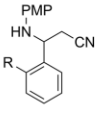
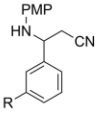
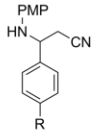
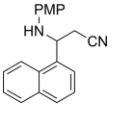
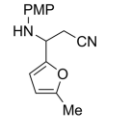
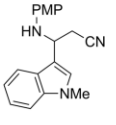
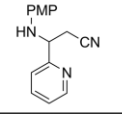


5, R^1 = H	0%	**11**, R^1 = R^2 = Me	0%
6, R^1 = Me	44%	**12**, R^1 = R^2 = OH	0%
		13, R^1 = CN, R^2 = Cl	28%
7, R^1 = R^2 = *t*Bu	8%	**14**, R^1 = Me, R^2 = OMe	6%
8, R^1 = R^2 = OH	24%	**15**, R^1 = R^2 = OMe	13%
9, R^1 = Me, R^2 = NHPh	60%	**16**, R^1 = R^2 = Me	30%
10, R^1 = *t*Bu, R^2 = OMe	28%	**2**, R^1 = R^2 = *t*Bu	80%
1, R^1 = *t*Bu, R^2 = OH	99%	**2**, R^1 = R^2 = *t*Bu	97%[b]

[a] Yields determined by ^{1}H NMR spectroscopy by using an internal standard. [b] Reaction run at 0.625 M concentration.

Table 2. Amine scope by using a ketene imine nucleophile.



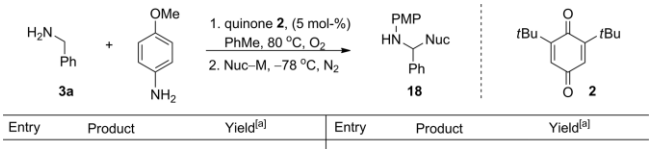
Entry	Product	Yield[a]
1		**17a**, R = H, 88%
2[b]		**17b**, R = Me, 82%
3		**17c**, R = OMe, 73%
4		**17d**, R = Me, 85%
5		**17e**, R = OMe, 70%
6		**17f**, R = Me, 90%
7		**17g**, R = Cl, 85%
8		**17h**, R = F, 79%
9		**17i**, R = CF_3, 89%
10		**17j**, 82%
11[c]		**17k**, 70%
12[c]		**17l**, 89%
13[c]		**17m**, 71%

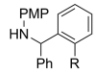
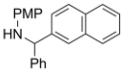
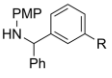
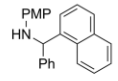
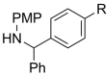
[a] Isolated yields. [b] With 20 mol-% of catalyst **2**. [c] With 10 mol-% of catalyst **2**.

was well tolerated under these conditions. When benzylamine was employed, the corresponding nitrile was obtained in 88 % yield (entry 1). Substitution at the *ortho*-position of the amine substrate resulted in a reduced reaction efficiency (entry 2, 82 % yield) compared to *meta*- and *para*-substitution (entries 4 and 6, 85 and 90 % yield, respectively). Electron-donating and electron-withdrawing substituents were compatible (entries 3, 5 and 7–9, 70–89 % yield) and showed no apparent trends with respect to the reaction efficiency. Heteroarylamines were also competent substrates, providing the corresponding nitriles in good yields when 10 mol-% of the catalyst was employed (entries 11–13, 70–89 % yield). A limitation of the present method for amine functionalization is that aliphatic amines, α-branched amines, and secondary amines failed to undergo the requisite oxidation under the current reaction conditions.

Next, the scope of the nucleophilic reaction partner was examined (Table 3). By using aryllithium reagents,[28] a variety of medicinally relevant benzhydrylamine derivatives[29] were generated from benzylamine in good yields (entries 1–9, 70–84 % yield). N-PMP benzhydrylamine can be synthesized in good yield by using this protocol (entry 1, 77 % yield). Substitution of a methyl substituent at the *ortho*-position of the nucleophile (entry 2, 78 % yield) resulted in a slightly diminished reaction efficiency compared to *meta*- and *para*-substitution (entries 4 and 5, 81 % and 84 %, respectively); however, steric effects seemed to have very little impact when employing isomeric 1- and 2-naphthyl nucleophiles (entries 8 and 9, 81 and 82 %, respectively). Aryl nucleophiles with electron-donating and electron-withdrawing substituents were also competent reaction partners (entries 3, 6, and 7, 70–80 % yield). α-Branched amines bearing an α-Csp^3 substituent also underwent formal oxidative alkylation (entries 10–12, 71–89 % yield) and allylation (entry 12, 84 %) reactions.

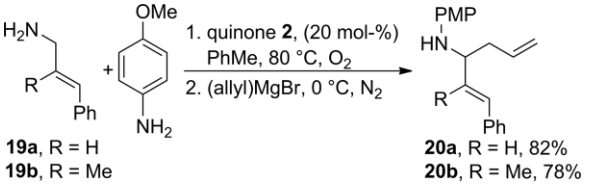
Table 3. Nucleophile scope by using benzylamine.



Entry	Product	Yield[a]	Entry	Product	Yield[a]
1[b,c]		**18a**, R = H, 77%	8[b]		**18h**, 81%
2[b]		**18b**, R = Me, 78%			
3[b]		**18c**, R = OMe, 80%			
4[b]		**18d**, R = Me, 81%	9[b]		**18i**, 82%
5[b]		**18e**, R = Me, 84%	10[b]		**18j**, Nuc = cyclopropyl, 71%
6[b]		**18f**, R = OMe, 70%	11[b,c]		**18k**, Nuc = *n*Bu, 77%
7[b]		**18g**, R = F, 72%	12[b,c]		**18l**, Nuc = Me, 89%
			13[c,d]		**18m**, Nuc = allyl, 84%

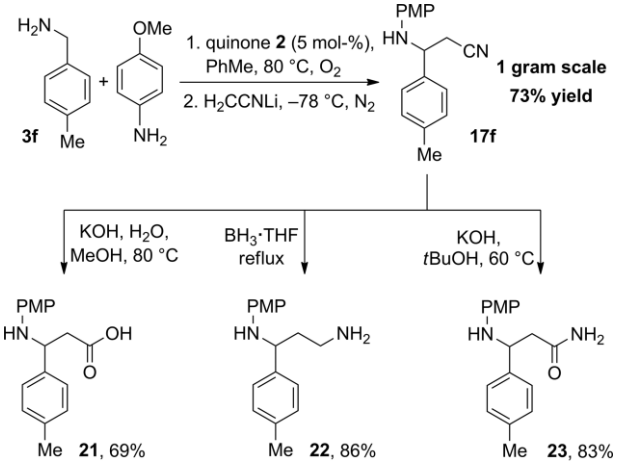
[a] Isolated yields. [b] Organolithium nucleophile used. [c] Nuc–M added at 0 °C. [d] Organomagnesium bromide nucleophile used.

Allylic amines were also suitable substrates (Scheme 3). By using 20 mol-% of the catalyst, both di- and tri-substituted primary allylic amines were well tolerated in reactions by using allylmagnesium bromide as the nucleophilic reaction partner (82 and 78 % yield, respectively). To the best of our knowledge, this is the first example of allylic amines being utilized in quinone-catalyzed oxidations.



Scheme 3. Application to allylic amine substrates.

This new protocol for formal amine functionalization also remained efficient when employed on a gram-scale and the resulting products represent useful synthetic building blocks (Scheme 4).[30] When 4-methylbenzylamine was used as a substrate under the optimized conditions for ketene imine addition on a gram-scale, nitrile **17f** was isolated in a slightly diminished yield of 73 %. Nitrile **17f** was readily converted to β-amino acid **21** in 69 % yield by using methanolic potassium hydroxide; β-amino acids of this type are commonly employed in the synthesis of β-lactams and peptidomimetics.[31] Reduction of **17f** with a borane-tetrahydrofuran complex delivered the corresponding diamine **22** in 86 % yield. Finally, **17f** was treated with potassium hydroxide in *tert*-butanol to afford amino amide **23** in 83 % yield.



Scheme 4. Gram-scale reaction and product utility.

Conclusions

In conclusion, we have developed a simple and efficient method for the preparation of α-branched amines through a sequential quinone-promoted amine oxidation/nucleophilic addition process. This new protocol provides access to versatile amine products in good to excellent yields (70–90 %). Amine substrates are currently limited to benzylic and allylic amines; future work will include the development of new quinone catalysts that will enable the oxidative functionalization of aliphatic amines.

Experimental Section

General Experimental Information: All reactions were carried out in flame-dried glassware with magnetic stirring unless otherwise stated. Toluene, THF, acetonitrile, and DCM were purified by passage through a bed of activated alumina.[32] Diisoproplyamine was distilled from calcium hydride[33] under nitrogen immediately prior to use. Commercially available aryl bromides were distilled prior to use. Purification of reaction products was carried out by flash chromatography using Fisher Chemical silica gel (230–400 Mesh, Grade 60). Analytical thin layer chromatography (TLC) was performed on EMD millipore TLC silica gel 60 – F 254: 25 glass plates. Visualization was accomplished with UV light and/or phosphomolybdic acid staining followed by heating. Melting point data were recorded using a Digimelt SRS. Film, NaCl pellet, or KBr pellet infrared spectra were recorded using a Shimadzu FTIR-8400S. ^{1}H NMR spectra were recorded on a Bruker Advance 400 (400 MHz) or a Bruker 500 (500 MHz) spectrometer and are reported in ppm using the solvent as a reference (residual $CHCl_3$ at δ = 7.26 ppm). Data are reported as (app = apparent, obs = obscured, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; integration; coupling constant(s) in Hz). Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker 500 (125 MHz) spectrometer and are reported in ppm using the solvent as a reference ($CDCl_3$ at δ = 77.16 ppm). Mass spectra data were obtained on a Micromass Ltd. LCT Premier quadrupole and time-of-flight tandem mass analyzer.

Sequential Amine Oxidation/Nucleophilic Addition; General Procedures

Procedure A: General Amine Oxidation (17, 18, and 20): To a solution of 2,6-di-*tert*-butyl-1,4-benzoquinone (5.5 mg, 0.025 mmol, unless otherwise noted) and *p*-anisidine (123.1 mg, 1.0 mmol) in toluene (800 μL, 0.625 M with respect to the amine substrate) was added the amine (0.50 mmol), followed by purging the reaction vial with a balloon of O_2. The reaction mixture was allowed to stir under O_2 at 80 °C for 24 h.

Procedure B: General Nucleophilic Addition for the Synthesis of β-Amino Nitriles (17a–17m): To a flame dried round-bottomed flask under N_2 was added THF (12.5 mL) and diisopropylamine (410 μL, 2.92 mmol); the solution was cooled to 0 °C. Then, *n*-butyllithium (2.62 mmol, 1.6 M solution in hexanes) was added dropwise. The solution was warmed to room temperature and stirred for 30 min. Then, the solution was cooled to –78 °C and acetonitrile (130.5 μL, 2.5 mmol) was added dropwise. After the addition, the reaction was warmed to room temperature and stirred for 15 min. Then, the solution was cooled again to –78 °C and the product of amine oxidation (see **Procedure A: General Amine Oxidation**) was added by using a cannula (followed by rinsing with toluene, 3 × 0.20 mL). At –78 °C, the reaction was monitored by TLC until the imine was consumed (typically between 30 min and 1 h) and then quenched by the addition of saturated aq. NH_4Cl (1.5 mL). The mixture was transferred to a separatory funnel by the aid of EtOAc; saturated aq. $NaHCO_3$ (3.0 mL) was added, the mixture was shaken vigorously, and the organic layer was collected. The aqueous layer was further extracted by using EtOAc (3 × 15 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography on silica gel provided the desired nitriles (**17a**–**17m**).[27]

Procedure C. General Nucleophilic Addition for the Synthesis of α-Substituted Benzylamines by Using Organolithium Nucleophiles Prepared in Situ (18b–18j): To a flame dried 25 mL round-bottomed flask under N_2 were added the corresponding arylbromide (1.5 mmol) and dry THF (5.0 mL). The solution was cooled to –78 °C and then *tert*-butyllithium (3.0 mmol, 1.7 M solution in pentane) was added dropwise under vigorous stirring. The reaction mixture was allowed to stir at –78 °C for 1 h. Then, the solution was warmed to room temperature and the product of amine oxidation (see **Procedure A: General Oxidation**) was added dropwise by using cannula (followed by rinsing with THF, 2 × 1.0 mL). The resulting solution was allowed to stir overnight and then quenched by slow addition of saturated aq. NH_4Cl (2.0 mL) followed by saturated aq. $NaHCO_3$ (4.0 mL). The mixture was transferred to a separatory funnel by the aid of Et_2O, shaken vigorously, and the organic phase was collected. The aqueous phase was further extracted with Et_2O (3 × 5.0 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography on silica gel provided the desired arylamines (**18b**–**18j**).[28]

Procedure D: General Nucleophilic Addition for the Synthesis of α-Substituted Benzylamines by Using Commercially Available Aryllithium (or Grignard) Reagents as Nucleophiles (18a, 18k–18m, and 20a–20b): The vial containing the product of amine oxidation (see **Procedure A: General Oxidation**) was purged with nitrogen and cooled to 0 °C. The organolithium reagent or the Grignard reagent (1.5 mmol) was added dropwise under N_2 atmosphere and vigorous stirring. Then, the mixture was warmed to room temperature and allowed to stir overnight and then quenched by slow addition of saturated aq. NH_4Cl (2.0 mL) followed by saturated aq. $NaHCO_3$ (4.0 mL). The mixture was transferred to a separatory funnel by the aid of Et_2O, shaken vigorously, and the organic phase was collected. The aqueous phase was further extracted with Et_2O (3 × 5.0 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) provided the desired amines (**18a**, **18k**–**18m**, **20a**–**20b**).

3-[(4-Methoxyphenyl)amino]-3-phenylpropanenitrile (17a): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17a** (98.2 mg, 88 %) as a brown oil, which was spectroscopically identical to previous reports.[34]

3-[(4-Methoxyphenyl)amino]-3-(o-tolyl)propanenitrile (17b): The reaction was carried out according to the general oxidation procedure **(A)** by using 2-methylbenzylamine (62 μL, 0.50 mmol) while employing a 20 mol-% loading of 2,6-di-*tert*-butyl-1,4-benzoquinone (22 mg, 0.10 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17b** (103.8 mg, 82 %) as a brown oil. IR (film): $\tilde{\nu}$ = 3379, 2993, 2833, 2248, 1228 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.41 (m, 1 H), 7.27–7.18 (m, 3 H), 6.78–6.70 (m, 2 H), 6.54 (d, *J* = 8.4 Hz, 2 H), 4.90 (t, *J* = 6.2 Hz, 1 H), 3.91 (br. s, 1 H), 3.72 (s, 3 H), 2.94–2.77 (m, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.0, 139.9, 138.0, 135.3, 131.2, 128.3, 127.0, 125.0, 117.4, 115.3, 115.0, 55.8, 51.5, 24.7, 19.3 ppm. HMRS (ESI): calcd. for $C_{17}H_{19}N_2O$ $[M + H]^+$ 267.1497; found 267.1488.

3-(2-Methoxyphenyl)-3-[(4-methoxyphenyl)amino]propanenitrile (17c): The reaction was carried out according to the general oxidation procedure **(A)** by using 2-methoxybenzylamine (65 μL, 0.5 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17c** (102.8 mg, 73 %) as a brown solid, m.p. 84 °C. IR (NaCl): $\tilde{\nu}$ = 3373, 2933, 2835, 1240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, *J* = 7.5, 1.7 Hz, 1 H), 7.30–7.27 (m, 1 H), 6.94 (dd, *J* = 7.5,

1.0 Hz, 1 H), 6.92 (app d, *J* = 8.2 Hz, 1 H), 6.73 (app d, *J* = 8.9 Hz, 2 H), 6.57 (app d, *J* = 8.9 Hz, 2 H), 4.95 (app t, *J* = 6.1 Hz, 2 H), 4.22 (br. s,1 H), 3.91 (s, 3 H), 3.71 (s, 3 H), 2.97 (dd, *J* = 16.7, 5.9 Hz, 1 H), 2.88 (dd, *J* = 16.7, 6.3 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.7, 152.9, 140.1, 129.4, 127.7, 127.4, 121.2, 118.0, 115.7, 115.0, 110.8, 55.8, 55.5, 51.4, 24.5 ppm. HMRS (ESI): calcd. for $C_{17}H_{19}N_2O_2$ $[M + H]^+$ 283.1447; found 283.1443.

3-[(4-Methoxyphenyl)amino]-3-(m-tolyl)propanenitrile (17d): The reaction was carried out according to the general oxidation procedure **(A)** by using 3-methylbenylamine (63 µL, 0.50 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17d** (151.2 mg, 85 %) as a red-brown oil. IR (KBr): $\tilde{\nu}$ = 3386, 2927, 2248, 1236 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 2 H), 7.29–7.24 (m, 1 H), 7.22–7.18 (m, 1 H), 6.75 (app d, *J* = 8.9 Hz, 2 H), 6.75 (app d, *J* = 9.0 Hz, 2 H), 4.67–4.60 (m, 1 H), 3.91 (br. s, 1 H), 3.72 (s, 3 H), 2.92–2.81 (m, 2 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.1, 140.2, 139.9, 139.0, 129.3, 129.1, 127.0, 123.4, 117.4, 115.74, 115.03, 55.8, 55.6, 26.4, 21.7 ppm. HMRS (ESI): calcd. for $C_{17}H_{19}N_2O$ $[M + H]^+$ 267.1497; found 267.1464.

3-(3-Methoxyphenyl)-3-[(4-methoxyphenyl)amino]propanenitrile (17e): The reaction was carried out according to the general oxidation procedure **(A)** by using 3-methoxybenzylamine (64 µL, 0.5 mmol), followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17e** (99.4 mg, 70 %) as a yellow oil. IR (NaCl): $\tilde{\nu}$ = 3371, 2935, 2835, 1240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (app t, *J* = 7.9 Hz, 1 H), 7.00–6.97 (m, 1 H), 6.96–6.93 (m, 1 H), 6.87–6.6.83 (m, 1 H), 6.74 (app d, *J* = 9.0 Hz, 2 H), 6.58 (app d, *J* = 9.0 Hz, 2 H), 4.66–4.61 (m, 1 H), 3.93 (br. s,1 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 2.89 (dd, *J* = 16.7, 6.1 Hz, 1 H), 2.84 (dd, *J* = 16.7, 6.1 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.3, 153.2, 142.0, 139.8, 130.4, 118.5, 117.3, 115.8, 115.75, 115.0, 113.7, 112.2 ppm. HMRS (ESI): calcd. for $C_{17}H_{19}N_2O_2$ $[M + H]^+$ 283.1447; found 283.1442.

3-[(4-Methoxyphenyl)amino]-3-(p-tolyl)propanenitrile (17f): The reaction was carried out according to the general oxidation procedure **(A)** by using 4-methylbenzylamine (64 µL, 0.50 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17f** (119.7 mg, 90 %) as a brown oil. IR (KBr): $\tilde{\nu}$ = 3367, 2950, 2248, 1035 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (app d, *J* = 8.1 Hz, 2 H), 7.18 (d, *J* = 7.8 Hz, 2 H) 6.74 (app d, *J* = 8.9 Hz, 2 H), 6.70–6.60 (m, 2 H), 4.65–4.59 (m, 1 H), 3.81. (s, 1 H), 3.72 (s, 3 H), 2.95 (br. s, 2 H), 2.64 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.1, 139.9, 138.3, 137.2, 129.9, 126.2, 117.4, 115.8, 115.0, 55.8, 55.3, 26.5, 21.3 ppm. HMRS (ESI): calcd. for $C_{17}H_{19}N_2O$ $[M + H]^+$ 267.1497; found 267.1477.

3-(4-Chlorophenyl)-3-[(4-methoxyphenyl)amino]propanenitrile (17g): The reaction was carried out according to the general oxidation procedure **(A)** by using 4-chlorobenzylylamine (61 µL, 0.50 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17g** (121.5 mg, 85 %) as a brown oil. IR (KBr): $\tilde{\nu}$ = 3373, 2933, 2833, 2248, 1203 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (s, 4 H), 6.74 (app d, *J* = 8.8 Hz, 2 H), 6.55 (app d, *J* = 9.0 Hz, 2 H), 4.68–4.63 (m, 1 H), 3.90 (br. s, 1 H), 3.71 (s, 3 H), 2.92–2.79 (m, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.3, 139.4, 138.7, 134.4, 129.5, 127.78, 117.0, 115.9, 115.0, 55.8, 54.9, 26.6 ppm. HMRS (ESI): calcd. for $C_{16}H_{16}ClN_2O$ $[M + H]^+$ 287.0951; found 287.0924.

3-(4-Fluorophenyl)-3-[(4-methoxyphenyl)amino]propanenitrile (17h): The reaction was carried out according to the general oxidation procedure **(A)** by using 4-fluorobenzylamine (57 µL, 0.50 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17h** (106.6 mg, 79 %) as a brown oil. IR (KBr): $\tilde{\nu}$ = 3369, 2933, 2833, 2248, 1236 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 8.5, 5.2 Hz, 2 H), 7.07 (app t, *J* = 8.5 Hz, 2 H), 6.74 (app d, *J* = 8.9 Hz, 2 H), 6.55 (app d, *J* = 8.9 Hz, 2 H), 4.70–4.62 (m, 1 H), 3.90 (br. s, 1 H), 3.72 (s,3 H), 2.92–2.78 (m, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.68 (d, *J* = 246.2 Hz), 163.66, 161.70, 139.5, 135.9 (d, *J* = 3.1 Hz), 128.1 (d, *J* = 8.3 Hz, 1 H), 117.1, 116.2 (d, *J* = 21.8 Hz), 115.9, 115.0, 55.8, 54.9, 26.6 ppm. HMRS (ESI): calcd. for $C_{17}H_{19}N_2O$ $[M + H]^+$ 271.1247; found 271.1229.

3-[(4-Methoxyphenyl)amino]-3-[4(trifluoromethyl)phenyl]-propanenitrile (17i): The reaction was carried out according to the general oxidation procedure **(A)** by using 4-(trifluoromethyl)benzylamine (71 µL, 0.50 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17i** (142.2 mg, 89 %) as a yellow oil. IR (KBr): $\tilde{\nu}$ = 3379, 2935, 2837, 2250, 1230 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.3 Hz, 2 H), 7.55 (d, *J* = 8.3 Hz, 2 H), 6.74 (d, *J* = 8.8 Hz, 2 H), 6.55 (d, *J* = 8.8 Hz, 2 H), 4.74 (q, *J* = 5.6 Hz, 1 H), 3.97 (d, *J* = 6.5 Hz, 1 H), 3.72 (s,3 H), 2.89 (dd, *J* = 6.0, 4.9 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.6, 144.4, 139. 5, 130.1 (q, *J* = 32.6 Hz, 1 H), 126.3 (q, *J* = 3.7 Hz, 2 H), 123.8 (q, *J* = 272.1 Hz, 1 H), 117.0, 116.1, 115.3, 56.0, 55.3, 26.7 ppm. HMRS (ESI): calcd. for $C_{17}H_{16}F_3N_2O$ $[M + H]^+$ 321.1215; found 321.1176.

3-[(4-Methoxyphenyl)amino]-3-(naphthalen-1-yl)propanenitrile (17j): The reaction was carried out according to the general oxidation procedure **(A)** by using 1-naphthylamine (62 µL, 0.5 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17j** (123.8 mg, 82 %) as a yellow oil. IR (KBr): $\tilde{\nu}$ = 3373, 3042, 2930, 2247, 1512, 1240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.2 Hz, 1 H), 7.94 (d, *J* = 8.9 Hz, 1 H), 7.84 (d, *J* = 8.2 Hz, 1 H), 7.68 (d, *J* = 7.2 Hz, 1 H), 7.62–7.52 (m, 2 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 6.73 (d, *J* = 8.9 Hz, 1 H), 6.57 (d, *J* = 8.9 Hz, 1 H), 5.50 (q, *J* = 6.6 Hz, 1 H), 4.13 (d, *J* = 5.9 Hz, 1 H) 3.70 (s, 3 H), 3.15 (dd, *J* = 17.0, 4.5 Hz, 1 H) 2.96 (dd, *J* = 17.0, 4.5 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.9, 139.7, 134.7, 134.2, 130.4, 129.5, 129.0, 127.0, 126.0, 125.7, 123.4, 121.7, 117.2, 115.2, 114.9, 55.7, 51.0, 25.1 ppm. HMRS (ESI): calcd. for $C_{20}H_{18}N_2O$ $[M + Li]^+$ 309.1579; found 309.1673.

3-[(4-Methoxyphenyl)amino]-3-(5-methylfuran-2-yl)propanenitrile (17k): The reaction was carried out according to the general oxidation procedure **(A)** by using 5-methylfurfurylamine (55 µL, 0.50 mmol) while employing a 10 mol-% loading of 2,6-di-*tert*-butyl-1,4-benzoquinone (11 mg, 0.050 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17k** (85.3 mg, 70 %) as a brown oil. IR (film): $\tilde{\nu}$ = 3352, 3107, 3033, 2997, 2833, 2248, 1272 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.82–6.77 (m, 2 H), 6.69–6.64 (m, 2 H), 6.21 (d, *J* = 3.1 Hz, 1 H), 5.92 (dq, *J* = 3.2, 1.1 Hz,1 H), 4.75 (t, *J* = 5.7 Hz, 1 H), 3.85–3.78 (br. s, 1 H), 3.75 (s, 3 H), 2.92–2.94 (m, 2 H), 2.28 (d, *J* = 1.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.7, 152.7, 150.5, 139.6, 117.5, 116.5, 115.3, 108.6, 106.8, 56.0, 50.5, 23.7,13.9 ppm. HMRS (ESI): calcd. for $C_{15}H_{17}N_2O_2$ $[M + H]^+$, 257.1290; found 257.1262.

3-[(4-Methoxyphenyl)amino]-3-(1-methyl-1*H*-indol-3-yl)propanenitrile (17l): The reaction was carried out according to the general oxidation procedure **(A)** by using 3-(aminomehyl)-1-methyindole (72 µL, 0.50 mmol) while employing 10 mol-% loading of 2,6-di-*tert*-butyl-1,4-benzoquinone (11 mg, 0.050 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (20 % ethyl acetate in hexanes) nitrile **17l** (134.3 mg, 88 %)

as a yellow oil. IR (KBr): $\tilde{\nu}$ = 3375, 2931, 2246, 1238 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.0 Hz, 1 H), 7.34 (d, J = 8.6 Hz, 1 H), 7.30–7.22 (m, 1 H), 7.22–7.13 (m, 1 H), 6.79 (d, J = 9.2 Hz, 2 H), 6.67 (d, J = 9.2 Hz, 2 H), 5.04 (d, J = 5.6 Hz, 1 H), 3.91 (d, J = 5.5 Hz, 1 H), 3.78 (s,3 H), 3.75 (s,3 H), 3.08 (dd, J = 16.5, 4.4 Hz, 1 H), 3.01 (dd, J = 16.5, 4.4 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.3, 140.4, 137.7, 126.9, 123.1, 122.6, 119.9, 119.1, 118.3, 115.7, 115.4, 113.9, 110.1, 56.1, 49.3, 33.3, 25.0 ppm. HMRS (ESI): calcd. for $C_{19}H_{19}N_3O$ $[M + H]^+$, 312.1688; found 312.1687.

3-[(4-Methoxyphenyl)amino]-3-(pyridin-2-yl)propanenitrile (17m): The reaction was carried out according to the general oxidation procedure **(A)** by using 2-picolylamine (52 μL, 0.50 mmol) while employing a 10 mol-% loading of 2,6-di-*tert*-butyl-1,4-benzoquinone (11 mg, 0.050 mmol) followed by the general addition procedure **(B)** to provide after purification on silica gel (30 % ethyl acetate in hexanes) nitrile **17m** (89.8 mg, 71 %) as a brown oil. IR (KBr): $\tilde{\nu}$ = 3352, 2954, 2831, 2246 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.64–8.61 (m, 1 H), 7.73–7.67 (m, 1 H), 7.40 (app d, J = 7.8 Hz, 1 H), 6.78 (app d, J = 8.8 Hz, 2 H), 6.65 (app d, J = 9.0 Hz, 2 H), 4.84–4.87 (m, 1 H), 4.50–4.40 (m, 1 H) 3.74 (s, 3 H), 3.06 (dd, J = 16.6, 5.1 Hz, 1 H), 2.93 (dd, J = 16.6, 7.1 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.2, 153.2, 150.0, 139.6, 137.2, 123.5, 122.2, 115.9, 115.2, 56.6, 55.8, 24.3 ppm. HMRS (ESI): calcd. for $C_{15}H_{16}N_3O$ $[M + H]^+$ 254.1293; found 254.1276.

***N*-Benzhydryl-4-methoxyaniline (18a):** The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(D)** by using phenyllithium (1.5 mmol, 1.8 M solution in dibutyl ether) to provide after purification on silica gel amine **18a** (112 mg, 77 %) as a brown oil, which is spectroscopically identical to previous reports.[35]

4-Methoxy-*N*-[phenyl(*o*-tolyl)methyl]aniline (18b): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(C)** by using 1-bromo-2-methylbenzene (0.18 mL, 1.5 mmol) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18b** (118 mg, 78 %) as a dark brown oil. IR (film): $\tilde{\nu}$ = 3382, 3101, 2948, 1228 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 6 H), 7.17 (m, 3 H), 6.76–6.68 (m, 2 H), 6.50–6.42 (m, 2 H), 5.57 (s, 1 H), 3.90 (br. s, 1 H), 3.71 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.2, 142.3, 141.9, 140.7, 136.0, 130.8, 128.7, 128.1, 127.4, 127.28, 127.27, 126.4, 114.8, 114.2, 60.2, 55.8, 19.6 ppm. HMRS (ESI): calcd. for $C_{21}H_{22}NO$ $[M + H]^+$ 304.1701; found 304.1672.

4-Methoxy-*N*-[(2-methoxyphenyl)(phenyl)methyl]aniline (18c): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(C)** by using 1-bromo-2-methoxybenzene (0.18 mL, 1.5 mmol) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18c** (127 mg, 80 %) as a red oil. IR (film): $\tilde{\nu}$ = 3406, 3062, 2933, 2833, 1290 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.34 (m, 3 H), 7.30 (m, 2 H), 7.25–7.19 (m, 2 H), 6.94–6.86 (m, 2 H), 6.74–6.68 (m, 2 H), 6.54–6.47 (m, 2 H), 5.81 (s, 1 H), 4.05 (br. s, 1 H), 3.79 (s, 3 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.1, 152.3, 143.5, 142.3, 131.4, 128.7, 128.6, 128.3, 127.8, 127.2, 121.1, 115.0, 114.9, 111.1, 57.6, 56.1, 55.8 ppm. HMRS (ESI): calcd. for $C_{21}H_{22}NO_2$ $[M + H]^+$ 320.1651; found 320.1612.

4-Methoxy-*N*-[phenyl(*m*-tolyl)methyl]aniline (18d): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(C)** by using 1-bromo-3-methylbenzene (0.18 mL, 1.5 mmol) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18d** (110 mg, 72 %) as a dark brown oil. IR (film): $\tilde{\nu}$ = 3296, 3197, 3089, 2829, 1247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 7.7 Hz, 2 H), 7.35–7.29 (m, 2 H), 7.26–7.13 (m, 4 H), 7.06 (d, J = 7.3 Hz, 1 H), 6.75–6.68 (m, 2 H), 6.54–6.47 (m, 2 H), 5.37 (s, 1 H), 3.99 (br. s, 1 H), 3.71 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.4, 143.6, 143.5, 142.1, 138.7, 129.0, 128.9, 128.4, 127.6, 127.5, 124.7, 115.0, 114.9, 64.2, 56.0, 21.8 ppm. HMRS (ESI): calcd. for $C_{21}H_{22}NO$ $[M + H]^+$ 304.1701; found 304.1676.

4-Methoxy-*N*-[phenyl(*p*-tolyl)methyl]aniline (18e): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(C)** by using 1-bromo-4-methylbenzene (0.18 mL, 1.5 mmol) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18e** (128 mg, 84 %) as a red oil, which is spectroscopically identical to previous reports.[36]

4-Methoxy-*N*-[(4-methoxyphenyl)(phenyl)methyl]aniline (18f): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(C)** by using 4-bromoanisole (0.19 mL, 1.5 mmol) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18f** (112 mg, 70 %) as a dark brown oil, which is spectroscopically identical to previous reports.[35]

***N*-[(4-Fluorophenyl)(phenyl)methyl]-4-methoxyaniline(18g):** The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(C)** by using 1-bromo-4-fluorobenzene (0.16 mL, 1.5 mmol) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18g** (110 mg, 72 %) as a brown oil. IR (film): $\tilde{\nu}$ = 3400, 3060, 3028, 2950, 1224 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.30 (m, 7 H), 7.06–6.95 (m, 2 H), 6.77–6.66 (m, 2 H), 6.55–6.42 (m, 2 H), 5.40 (s, 1 H), 3.95 (br. s, 1 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.2 (d, J = 247.0 Hz), 152.5, 143.3, 141.7, 139.2 (d, J = 2.5 Hz), 129.2 (d, J = 7.6 Hz), 129.1, 127.8, 127.7, 115.9, 115.8, 115.0 (d, J = 7.6 Hz), 63.4, 56.0 ppm. HMRS (ESI): calcd. for $C_{20}H_{18}FNO$ $[M]^+$ 307.1372; found 307.1368.

4-Methoxy-*N*-[naphthalen-2-yl(phenyl)methyl]aniline (18h): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(C)** by using 2-bromonaphthalene (310.6 mg, 1.5 mmol) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18h** (138 mg, 81 %) as a yellow oil, which is spectroscopically identical to previous reports.[35]

4-Methoxy-*N*-[naphthalen-1-yl(phenyl)methyl]aniline (18i): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(C)** by using 1-bromonaphthalene (0.21 mL, 1.5 mmol) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18i** (140 mg, 82 %) as a brown oil, which is spectroscopically identical to previous reports.[36]

***N*-[Cyclopropyl(phenyl)methyl]-4-methoxyaniline (18j):** The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(C)** by using bromocyclopropane (0.12 mL,

1.5 mmol) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18j** (90.5 mg, 71 %) as a brown oil, which is spectroscopically identical to previous reports.[37]

4-Methoxyphenyl(1-phenylpentyl)amine (18k): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.5 mmol) followed by the general addition procedure **(D)** by using *n*-butyllithium (1.6 M solution in hexanes) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **18k** (103 mg, 77 %) as a brown oil, which is spectroscopically identical to previous reports.[38]

4-Methoxy-*N*-(1-phenylethyl)aniline (18l): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(D)** by using methyllithium (1.5 mmol, 1.6 M solution in diethyl ether) to provide after purification on silica gel amine **18l** (101 mg, 89 %) as a brown oil, which is spectroscopically identical to previous reports.[39]

4-Methoxy-*N*-(1-phenylbut-3-en-1-yl)aniline (18m): The reaction was carried out according to the general oxidation procedure **(A)** by using benzylamine (55 μL, 0.50 mmol) followed by the general addition procedure **(D)** by using a solution of allylmagnesium bromide (1.5 mmol, 1.0 M solution in diethyl ether) to provide after purification on silica gel amine **18m** (107 mg, 84 %) as a red oil, which is spectroscopically identical to previous reports.[40]

(*E*)-4-Methoxy-*N*-(1-phenylhexa-1,5-dien-3-yl)aniline (20a): The reaction was carried out according to the general oxidation procedure **(A)** by using **19a**[41] (66.6 mg, 0.5 mmol) while employing a 20 mol-% loading of 2,6-di-*tert*-butyl-1,4-benzoquinone (22.4 mg, 0.1 mmol) followed by the general addition procedure (**D**) by using a solution of allylmagnesium bromide (1.5 mmol, 1.0 M solution in diethyl ether) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **20a** (114 mg, 82 %) as a red oil, which is spectroscopically identical to previous reports.[40]

(*E*)-4-Methoxy-*N*-(2-methyl-1-phenylhexa-1,5-dien-3-yl)aniline (20b): The reaction was carried out according to the general oxidation procedure **(A)** by using **19b**[41] (73.6 mg, 0.5 mmol) while employing a 20 mol-% loading of 2,6-di-*tert*-butyl-1,4-benzoquinone (22.4 mg, 0.1 mmol) followed by the general addition procedure (**D**) by using a solution of allylmagnesium bromide (1.5 mmol, 1.0 M solution in diethyl ether) to provide after purification on silica gel (10 % ethyl acetate in hexanes with 1 % triethylamine) amine **20b** (114 mg, 78 %) as red oil. IR (film): $\tilde{\nu}$ = 3398, 3024, 2831 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 3 H), 7.25–7.16 (m, 2 H), 6.77–6.72 (m, 2 H), 6.63–6.56 (m, 2 H), 6.56 (s, 1 H), 5.83 (dddd, *J* = 16.5, 10.1, 7.7, 6.4 Hz, 1 H), 5.23–5.10 (m, 2 H), 3.78 (dd, *J* = 7.9, 6.1 Hz, 1 H), 3.73 (s, 3 H), 2.56–2.35 (m, 2 H), 1.86 (d, *J* = 1.4 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.2, 142.1, 139.2, 138.2, 135.4, 129.2, 128.3, 126.5, 126.5, 118.1, 115.0, 114.9, 61.9, 56.0, 39.7, 14.5 ppm. HMRS (ESI): calcd. for $C_{20}H_{23}NO$ $[M]^+$ 293.1780; found 293.1793.

Gram-Scale Synthesis of Nitrile 17f and Its Derivatives (21–23)

3-[(4-Methoxyphenyl)amino]-3-(*p*-tolyl)propanenitrile (17f) (gram-scale preparation): The reaction was carried out according to the general oxidation procedure **(A)** by using 4-methylbenzylamine (640 μL, 5.0 mmol), *p*-anisidine (1.231 g, 10 mmol), and 2,6-di-*tert*-butyl-1,4-benzoquinone (55 mg, 0.25 mmol) followed by the general addition procedure (**B**) by using diisopropylamine (4.1 mL, 29.2 mmol), *n*-butyllithium (25 mmol, 1.6 M solution in hexanes), and acetonitrile (1.3 mL, 25 mmol) to provide after purification on silica gel (20 % ethyl acetate in hexanes) the nitrile **17f** (1.0353 g, 78 %) as a brown oil. (see characterization data above.).

3-[(4-Methoxyphenyl)amino]-3-(*p*-tolyl)propanoic acid (21):[30] To a flame dried round-bottomed flask was added **17e** (59 mg, 0.22 mmol), KOH (1.2 g), H_2O (8.0 mL), and MeOH (5.0 mL). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the volatiles were removed under vacuum and a solution of aq. 6 M HCl was added until pH = 3. The organic materials were extracted by using DCM (3 × 10 mL) and the combined layers were dried with $NaSO_4$ and concentrated under reduced pressure to afford the desired acid **21** (43.3 mg, 69 %) as a yellow solid, m.p. 57 °C. IR (film): $\tilde{\nu}$ = 3446, 3350, 2955, 2839, 1718, 1261 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 5.0 Hz, 2 H), 7.16–7.10 (m, 4 H), 6.80 (d, *J* = 5.0 Hz, 2 H), 4.65 (dd, *J* = 11.2, 3.0 Hz, 1 H), 3.85 (dd, *J* = 18.4, 10.7 Hz, 1 H), 3.77 (s, 3 H), 3.02 (dd, *J* = 18.6, 3.1 Hz, 1 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.1, 160.2, 140.3, 123.0, 129.1, 126.3, 125.2, 115.0, 100.1, 65.2, 55.7, 36.9, 21.4 ppm. HMRS (ESI): calcd. for $C_{17}H_{20}NO_3$ $[M + H]^+$ 286.1443; found 286.1426.

***N*^{1}-(4-Methoxyphenyl)-1-(*p*-tolyl)propane-1,3-diamine (22):**[30] To a solution of **17e** (67 mg, 0.25 mmol) in THF (1 mL) under N_2 atmosphere was added a solution of BH_3 in THF (0.75 mL, 0.75 mmol) at room temperature and a condenser was attached. After refluxing for 4.5 h, the reaction mixture was cooled to room temperature and aq. 6 M HCl (1.0 mL) was added before stirring for another 1 h. Then, the mixed solution was basified to pH 9 through the addition of aq. 3 M NaOH and the organic materials were extracted with DCM (3 × 15 mL). The combined layers were dried with Na_2SO_4 and concentrated under pressure to afford diamine **22** (58.1 mg, 86 %) as a pink oil. IR (film): $\tilde{\nu}$ = 3333, 2929, 2860, 1232 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.20 (m, 2 H), 7.14–7.09 (m, 2 H), 6.69–6.64 (m, 2 H), 6.49–6.45 (m, 2 H), 4.34 (t, *J* = 6.7 Hz, 1 H), 3.68 (s, 3 H), 2.88–2.76 (m, 2 H), 2.31 (s, 3 H), 1.89 (app q, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.9, 142.0, 141.4, 136.5, 129.4, 126.4, 114.9, 114.6, 57.8, 55.9, 42.0, 39.7, 21.2 ppm. HMRS (ESI): calcd. for $C_{17}H_{23}N_2O$ $[M + H]^+$ 271.1810; found 271.1772.

3-[(4-Methoxyphenyl)amino]-3-(*p*-tolyl)propanamide (23):[30] A mixture of **17e** (67 mg, 0.25 mmol) in *t*BuOH (5.0 mL) and KOH (210 mg) was stirred at 60 °C for 4 h. Then, H_2O (10 mL) was added and the organic materials were extracted with EtOAc (3 × 15 mL). The combined layers were dried with $NaSO_4$ and concentrated under reduced pressure. The crude mixture was further purified by column chromatography on silica gel (10 % methanol in DCM) to afford amide **23** (59.5 mg, 83 %) as a brown solid, m.p. 134 °C. IR (film): $\tilde{\nu}$ = 3342, 3151, 2926, 1662, 1236 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 2 H), 7.14–7.10 (m, 2 H), 6.72–6.68 (m, 2 H), 6.58–6.53 (m, 2 H), 4.68 (t, *J* = 6.5 Hz, 1 H), 3.69 (s, 3 H), 2.68 (d, *J* = 6.5 Hz, 2 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.0, 152.7, 140.8, 139.5, 137.2, 129.7, 126.2, 115.8, 114.9, 56.3, 55.8, 44.2, 21.2 ppm. HMRS (ESI): calcd. for $C_{17}H_{21}N_2O_2$ $[M + H]^+$ 285.1603; found 285.1621.

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[1] For a review on Gabriel-type amine alkylations, see: M. S. Gibson, R. W. Bradshaw, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 919; *Angew. Chem.* **1968**, *80*, 986.
[2] For selected reviews on reductive amination, see: a) M. Klussmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 7124; *Angew. Chem.* **2009**, *121*, 7260; b) T. C. Nugent, in *Chiral Amine Synthesis*; Wiley-VCH, Weinheim, **2010**, p. 225.
[3] For a selected review on imine addition reactions, see: S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069.
[4] For a selected review on hydroamination reactions see: T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795.
[5] For selected recent advances in hydroamination chemistry, see: a) S. Zhu, N. Niljianskul, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 15746; b) J. Gui, C.-M. Pan, Y. Jin, T. Qin, J. C. Lo, B. J. Lee, S. H. Spergel, M. E. Mertzman, W. J. Pitts, T. E. La Cruz, M. A. Schmidt, N. Darvatkar, S. R. Natarajan, P. S. Baran, *Science* **2015**, *348*, 886; c) Y. Yang, S.-L. Shi, D. Niu, P. Liu, S. L. Buchwald, *Science* **2015**, *349*, 62.
[6] For selected advances in C–H amination, see: a) C. G. Espino, P. M. Wehn, J. Chow, J. Du Bois, *J. Am. Chem. Soc.* **2001**, *123*, 6935; b) S. M. Paradine, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 2036; c) J. L. Roizen, D. N. Zalatan, J. Du Bois, *Angew. Chem. Int. Ed.* **2013**, *52*, 11343; *Angew. Chem.* **2013**, *125*, 11553.
[7] a) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114; b) A. Noble, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 11602; c) C. K. Prier, D. W. C. MacMillan, *Chem. Sci.* **2014**, *5*, 4173.
[8] a) D. B. Freeman, L. Furst, A. G. Condie, C. R. J. Stephenson, *Org. Lett.* **2012**, *14*, 94; b) G. R. Stephenson, C. Roe, C. E. Anson, *J. Org. Chem.* **2012**, *77*, 9684; c) G. Bergonzini, C. S. Schindler, C.-J. Wallentin, E. N. Jacobsen, C. R. J. Stephenson, *Chem. Sci.* **2014**, *5*, 112.
[9] a) M. Rueping, D. Leonori, T. Poisson, *Chem. Commun.* **2011**, *47*, 9615; b) M. Rueping, S. Zhu, R. M. Koenigs, *Chem. Commun.* **2011**, *47*, 12709; c) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori, C. Vila, *Chem. Eur. J.* **2012**, *18*, 5170; d) G. Zhao, C. Yang, L. Guo, H. Sun, C. Chen, W. Xia, *Chem. Commun.* **2012**, *48*, 2337.
[10] For selected reviews, see: a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; b) J. W. Beatty, C. R. J. Stephenson, *Acc. Chem. Res.* **2015**, *48*, 1474.
[11] T.-Y. Chen, R. Tsutsumi, T. P. Montgomery, I. Volchkov, M. J. Krische, *J. Am. Chem. Soc.* **2015**, *137*, 1798.
[12] Y.-F. Cheng, H.-J. Rong, C.-B. Yi, J.-J. Yao, J. Qu, *Org. Lett.* **2015**, *17*, 4756.
[13] J. M. Allen, T. H. Lambert, *J. Am. Chem. Soc.* **2011**, *133*, 1260.
[14] K. Kiyokawa, T. Kosaka, T. Kojima, S. Minakata, *Angew. Chem. Int. Ed.* **2015**, *54*, 13719; *Angew. Chem.* **2015**, *127*, 13923.
[15] For selected examples, see: a) S.-I. Murahashi, N. Komiya, H. Terai, *Angew. Chem. Int. Ed.* **2005**, *44*, 6931; *Angew. Chem.* **2005**, *117*, 7091; b) T. Sonobe, K. Oisaki, M. Kanai, *Chem. Sci.* **2012**, *3*, 3249.
[16] For a selected review on dehydrogenative cross-coupling in amine functionalization, see: C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335.
[17] For an example of α-functionalization of primary amines, see: D. B. Ushakov, K. Gilmore, D. Kopetzki, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2014**, *53*, 557; *Angew. Chem.* **2014**, *126*, 568.
[18] For selected reviews, see: a) J. P. Klinman, *J. Biol. Chem.* **1996**, *271*, 27189; b) M. Mure, *Acc. Chem. Res.* **2004**, *37*, 131.
[19] E. J. Corey, K. Achiwa, *J. Am. Chem. Soc.* **1969**, *91*, 1429.
[20] For metal-catalyzed variants by using quinone co-catalysts, see: a) M. Mure, J. P. Klinman, *J. Am. Chem. Soc.* **1993**, *115*, 7117; b) M. Mure, J. P. Klinman, *J. Am. Chem. Soc.* **1995**, *117*, 8698; c) M. Mure, J. P. Klinman, *J. Am. Chem. Soc.* **1995**, *117*, 8707.
[21] For a selected review on related oxidations, see: a) A. E. Wendlandt, S. S. Stahl, *Org. Lett.* **2012**, *14*, 2850; b) A. E. Wendlandt, S. S. Stahl, *J. Am. Chem. Soc.* **2014**, *136*, 11910; c) A. E. Wendlandt, S. S. Stahl, *Angew. Chem. Int. Ed.* **2015**, *54*, 14638; *Angew. Chem.* **2015**, *127*, 14848.
[22] Y. Qin, L. Zhang, J. Lv, S. Luo, J.-P. Cheng, *Org. Lett.* **2015**, *17*, 1469.
[23] For metal-catalyzed variants by using quinone co-catalysts, see: a) M. Largeron, M.-B. Fleury, *Angew. Chem. Int. Ed.* **2012**, *51*, 5409; *Angew. Chem.* **2012**, *124*, 5505; b) H. Yuan, W.-J. Yoo, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, *134*, 13970; c) M. Largeron, M.-B. Fleury, *Chem. Eur. J.* **2015**, *21*, 3815.
[24] For a selected review on related oxidations, see: B. Chen, L. Wang, S. Gao, *ACS Catal.* **2015**, *5*, 5851.
[25] Quinone 1 can be made in two steps from resorcinol; see ref.[21a]
[26] J. S. Yadav, B. V. S. Reddy, T. Swamy, K. S. Shankar, *Monatsh. Chem.* **2008**, *139*, 1317.
[27] G. R. Lawton, H. Ji, P. Martasek, L. J. Roman, R. B. Silverman, *Beilstein J. Org. Chem.* **2009**, *5*, No. 28.
[28] M. Giannerini, M. Fañanás-Mastral, B. L. Feringa, *Nat. Chem.* **2013**, *5*, 667.
[29] a) L. Juhlin, C. De Vos, J. P. Rihoux, *J. Allergy Clin. Immunol.* **1987**, *80*, 599; b) C. De Vos, M. R. Maleux, E. Baltes, J. Gobert, *Ann. Allergy* **1987**, *59*, 278.
[30] B. Rao, X. Zeng, *Org. Lett.* **2014**, *16*, 314.
[31] For selected reviews on β-amino acids, see: a) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219; b) C. Cabrele, T. A. Martinek, O. Reiser, Ł. Berlicki, *J. Med. Chem.* **2014**, *57*, 9718; c) F. Kudo, A. Miyanaga, T. Eguchi, *Nat. Prod. Rep.* **2014**, *31*, 1056.
[32] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.
[33] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals. 3rd Ed*; Pergamon Press, **1988**.
[34] T. Poisson, V. Gembus, S. Oudeyer, F. Marsais, V. Levacher, *J. Org. Chem.* **2009**, *74*, 3516.
[35] A. Yu, Y. Wu, B. Cheng, K. Wei, J. Li, *Adv. Synth. Catal.* **2009**, *351*, 767.
[36] N. Cabello, J.-C. Kizirian, S. Gille, A. Alexakis, G. Bernardinelli, L. Pinchard, J.-C. Caille, *Eur. J. Org. Chem.* **2005**, 4835.
[37] C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450.
[38] C. Denhez, J.-L. Vasse, J. Szymoniak, *Synthesis* **2005**, 2075.
[39] H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov, X. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 12100.
[40] M. Shimizu, M. Kimura, T. Watanabe, Y. Tamaru, *Org. Lett.* **2005**, *7*, 637.
[41] Prepared according to: a) E. Pavlakos, T. Georgiou, M. Tofi, T. Montagnon, G. Vassilikogiannakis, *Org. Lett.* **2009**, *11*, 4556; b) A. Jaganathan, A. Garzan, D. C. Whitehead, R. J. Staples, B. Borhan, *Angew. Chem. Int. Ed.* **2011**, *50*, 2593; *Angew. Chem.* **2011**, *123*, 2641; c) K.-B. Wang, R.-Q. Ran, S.-D. Xiu, C.-Y. Li, *Org. Lett.* **2013**, *15*, 2374.

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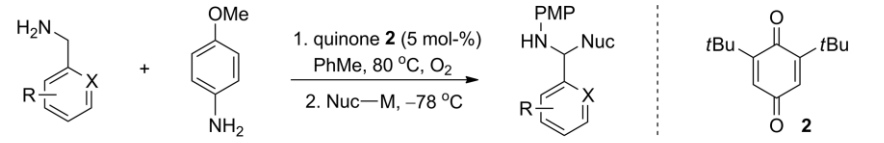

■ 27 substrates, 70–90% yield ■ commercially available quinone catalyst ■ versatile amine products

A new method for the synthesis of α-branched amines through formal oxidative C–H functionalization is reported. A commercially available quinone organocatalyst is employed to promote the aerobic oxidation of a primary amine substrate to the corresponding N-protected imine, which is then trapped in situ with an appropriate nucleophilic reaction partner to deliver functionalized amine products.

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