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Tf_2NH-Catalyzed 1,6-Conjugate Addition of Vinyl Azides with *p*-Quinone Methides: A Mild and Efficient Method for the Synthesis of β-Bis-Arylamides

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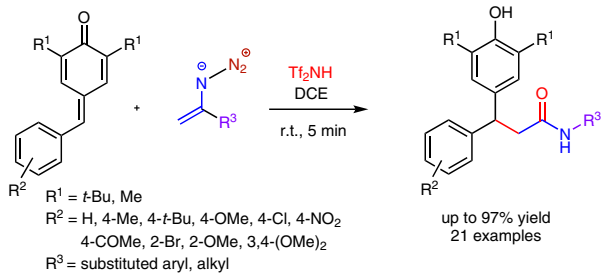

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Abstract Tf_2NH-catalyzed tandem 1,6-conjugate addition/Schmidt type rearrangement using vinyl azides and *p*-quinone methides to access a variety of β-bis-arylated amides is reported. The method is quick, efficient, mild, and high yielding with broad substrate scope.

Key words vinyl azide, *p*-quinone methide, Brønsted acid, 1,6-conjugate addition, rearrangement, β-bis-arylamides

The β-bis-arylamides framework is a privileged structure embedded in various pharmaceutically active drugs and natural products (Figure 1). The bio-significance of β-bis-aryl amides propelled extensive endeavor towards their synthesis and development of novel and scalable protocols. Various synthetic approaches for β-bis-aryl amides have been documented in the literature,[1] however, the majority of them suffer either from the use of transition metal and expensive metal catalyst, long reaction times, harsh reaction conditions, and tedious workup. Therefore, development of mild and metal-free catalytic conditions for this reaction is highly desirable.

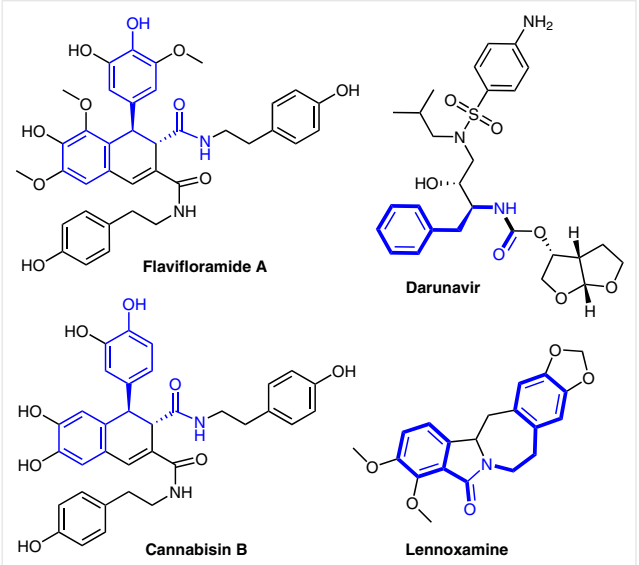


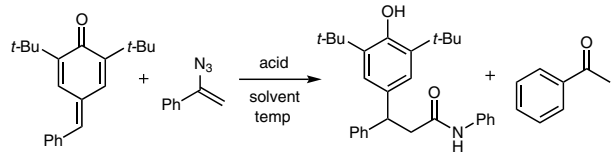
Figure 1 Privileged pharmaceutically active and naturally occurring amides

In recent years, the *p*-quinone methide derivatives gained attraction among synthetic organic chemistry, due to its unique reactivity[2] and its ability for 1,6-conjugate addition with a variety of nucleophiles.[3] *p*-Quinone methide motif serves as an important reactive intermediate in various natural product syntheses[4] and biosynthetic transformations.[5] Recently, *p*-quinone methides (*p*-QMs) were extensively studied for addition reaction, using the Lewis acid, organocatalytic, and transition-metal-catalyzed transformations.[6] Anand and co-workers have thoroughly investigated the chemistry of *p*-quinone methides for 1,6-conjugate addition with a variety of nucleophiles[7] using Lewis acid, N-heterocyclic carbene, bis(amino)cyclopropenylidene, and transition metal as a catalyst. Fan, Tortosa, and their co-workers including many other groups have studied the asymmetric Michael addition of *p*-quinone methides with malonates, enamines, borane thioester, and glycine Schiff base.[8,9] Lin and co-workers independently studied the reaction of *p*-quinone methide[10] catalyzed by the Lewis acid for the construction of unsymmetrical triarylmethanes.[10a] Bifunctional Pd complex and thiourea-catalyzed [3 + 2] annulation of *p*-QMs and vinylcyclopropanes is reported to give spirocycles with excellent diastereoselectivity.[10b] Construction of spirocycles via tandem 1,6-addition/cyclization with vinyl *p*-QMs was reported by Fan and

co-workers and also by Yao et al. using sulfonium salts,[11a] and α-halo diester,[11b] respectively. Recently Roiser and co-workers have reported the enantioselective spirocyclopropanation of *p*-QMs using ammonium ylides.[11c]

Vinyl azide has attracted a great deal of interest among synthetic chemists due to its chemical properties as a precursor for the construction of new C–C bond and various nitrogen containing heterocycles in the presence of Lewis/Brønsted acid activators.[12] The unique chemical reactivity of vinyl azide as an enamine type nucleophile,[13] is known to give amide via Schmidt type rearrangement.[14] These reports reveal that vinyl azide could serve as a good nucleophilic precursor for the amide under the mild reaction conditions. This inspired us to explore the reactivity of vinyl azide for conjugate addition reaction. We hypothesized that *p*-quinone methide could be a good counter-motif for the enamine type attack of vinyl azide resulting in the interesting β-bis-arylamide framework.

Table 1 Optimization of Reaction Conditions[a]



1a 2a 3a 4

Entry	Acid	Solvent	Time	Temp (°C)	Yield (%)[b]	
					3a	**4**
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	5 h	–40	65	18
2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	5 h	–30	56	25
3	$BF_3{\cdot}OEt_2$	CH_2Cl_2	5 h	0	30	63
4[c]	$BF_3{\cdot}OEt_2$	CH_2Cl_2	2 h	r.t.	trace	78
5[d]	$BF_3{\cdot}OEt_2$	CH_2Cl_2	1 h	r.t.	72	32
6[d,e]	Tf_2NH	DCE	30 min	0	82	43
7[d,e]	Tf_2NH	DCE	5 min	r.t.	89	46
8[d,f]	Tf_2NH	DCE	5 min	r.t.	85	39
9[d,f,g]	**Tf_2NH**	**DCE**	**5 min**	**r.t.**	**92**	**5**
10[d,f,g]	Tf_2NH	DCE	5 min	40	66	34
11[h]	$BF_3{\cdot}OEt_2$	DCE	1 h	r.t.	49	38

[a] Unless otherwise stated, the reaction was performed with *p*-quinone methide **1a** (0.034 mmol, 10 mg), H_2O (2 equiv), $BF_3{\cdot}OEt_2$ (2 equiv), and solvent (1 mL) by slow addition of a solution of vinyl azide **2a** (2 equiv) in solvent (2 mL).
[b] Isolated yields.
[c] Vinyl azide **2a** was directly added at once.
[d] Addition sequence of reagent was changed, in place of vinyl azide **2a**, the acid was added dropwise and the reaction was carried out without any additive (H_2O).
[e] Reaction was performed with 2 equiv of Tf_2NH.
[f] Tf_2NH used: 10 mol%.
[g] Phenyl vinyl azide used: 1.2 equiv.
[h] $BF_3{\cdot}OEt_2$ (10 mol%), H_2O (2 equiv), and phenyl vinyl azide (1.2 equiv) were used.

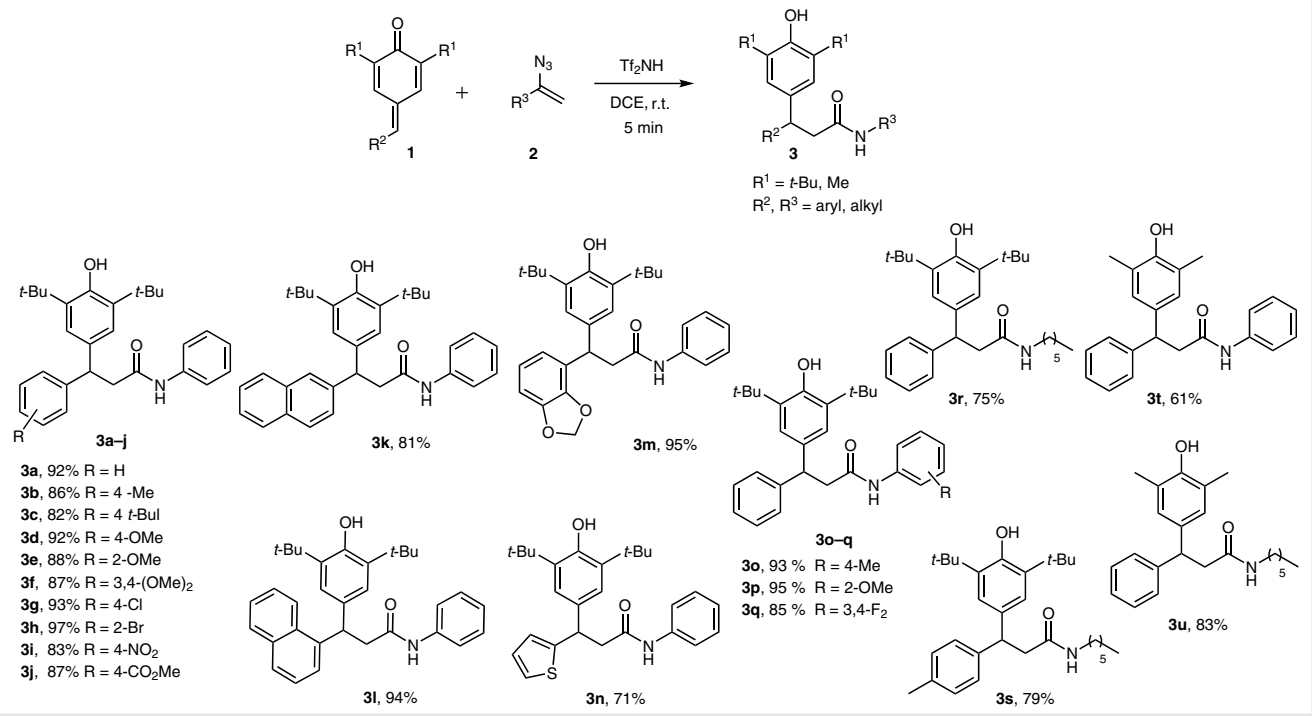
To investigate our hypothesis of the addition reaction of vinyl azide to the *p*-quinone methide, simple *p*-quinone methide **1a** and phenyl vinyl azide (**2a**) were chosen as model substrates. First the optimization of reaction conditions were conducted following the literature report by Chiba et al.[14a] for the 1,6-conjugate addition of vinyl azide and imines using $BF_3{\cdot}OEt_2$ and water as an additive in dichloromethane. However, the desired product **3a** was obtained in moderate yield (65%) only (Table 1, entry 1) along with other several by-products such as acetophenone and acetanilide. The other limitation of this method was the slow addition (5 h) of vinyl azide solution at –40 °C. In order to optimize the reaction conditions, the reaction was performed at a higher temperature like –30 °C, but the yield dropped to 56% (entry 2) with an increase in the formation of by-product. When the reaction was performed at 0 °C, the yield dropped to 30%, and acetophenone was obtained as a major by-product due to the self-hydrolysis of vinyl azide (entry 3). When the reaction was carried out at room temperature, only trace amount of the desired product was formed along with acetophenone as the major product (entry 4). From these observations, we reasoned that due to the presence of excess acid in the reaction medium, the simultaneous hydrolysis reaction of phenyl vinyl azide is the main competing reaction with the addition reaction at the higher temperature. To overcome these limitations, the reaction was further performed by changing the addition sequence of vinyl azide and $BF_3{\cdot}OEt_2$. Accordingly, *p*-quinone methide, vinyl azide, and water were taken in dichloromethane followed by slow addition of $BF_3{\cdot}OEt_2$ dropwise. The results obtained were as per our expectation, affording the desired product in 72% yield within 1 hour, with acetophenone as the side product (entry 5). With these results in hand, we further proceeded with improvement in the yield and switched over to bis (trifluoromethanesulfonyl)imide (triflimide, Tf_2NH) as the Brønsted acid. Gratifyingly, when the reaction was performed at 0 °C in dichloroethane (DCE), the reaction was complete within 30 minutes, and the desired product **3a** was obtained in excellent yield (82%) (entry 6). When the reaction was carried out at room temperature, it was complete within 5 minutes as confirmed by TLC. As per literature precedence,[15] we again examined the use of a catalytic amount of Tf_2NH. It was found that 10 mol% Tf_2NH was sufficient enough to bring out the above transformation within 5 minutes at room temperature to afford the desired product in excellent yield (89%) (entry 7). We further optimized the amount of vinyl azide **2a** used in the reaction as the excess amount of **2a** was always converted into acetophenone as a by-product. To reduce the formation of by-product, the reaction was performed with a slight excess (1.2 equiv) of vinyl azide **2a** affording the desired product in 92% yield with only minor amount of side product (entry 9). When the temperature was increased to 40 °C, the yield was diminished to 66% (entry 10). The reason for the low yield may be attributed to

the increase in the reaction temperature. This could result into the acceleration of self decomposition of vinyl azide **2a** to acetophenone thus reducing its availability for nucleophilic attack on *p*-quinone methide. In yet another reaction with catalytic amount of $BF_3{\cdot}OEt_2$ (10 mol %), the yield of the desired product **3a** was diminished to 49% with considerable amount of by-product (entry 11). While preparing this manuscript, a similar report of this reaction catalyzed by $BF_3{\cdot}OEt_2$as Lewis acid appeared in literature,[16] which exactly matches with our observation as made in the optimization reaction (see entry 5).

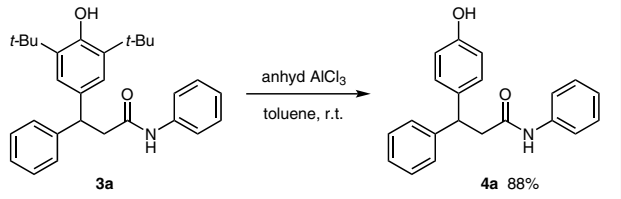
Having optimized the reaction condition, the substrate scope was examined next by varying the substitution R^2 on *p*-quinone methide **1** and R^3 in vinyl azide **2** (Scheme 1). First, *p*-quinone methides were screened with the different R^2 substitutions. For example, various 4-substituted *p*-quinone methide reacted smoothly with phenyl vinyl azide (**2a**) irrespective of the nature of substituents (electron-donating or -withdrawing) to give the respective amides in excellent yields. Similarly, the reaction was compatible even with variously substituted alkanes (Me, *t*-Bu), methoxy as electron-donating and chloro, bromo, nitro, ester as electron-withdrawing groups (**3a–j**). Under optimized conditions, the *ortho*, *meta*, and polysubstituted *p*-quinone methide also gave an excellent yield of products (**3e**, **3f**, and **3h**).

Moreover, the *p*-quinone methide with the fused aromatic and heterocyclic moieties like 1- and 2-naphthyl, thiophene, benzodioxole (Scheme 1, 3k–n) were also quite amenable under the optimized conditions (yields 71–95%). Besides, variously substituted phenyl vinyl azides were also screened to examine the generality of this developed protocol. As shown in Scheme 1, 4-methyl-, 2-methoxy-, and 3,4-difluoro-substituted phenyl vinyl azides reacted smoothly to deliver the desired products in excellent yields (**3o–q**). To establish the generality of the method, the reaction was further investigated with alkyl vinyl azide, which worked smoothly to give the products in good yields (**3r**, **s**). Interestingly the reaction of dimethyl-substituted *p*-QM with alkyl/phenyl vinyl azide gave the desired products in moderate to good yields (**3t–u**). The role of bulky substituents at 2 and 6-position of phenol such as *tert*-butyl group is crucial for the stability of *p*-QMs. As per the literature evidences, phenyl and methyl substituents also work well in stabilizing p-QMs. However, at our hand *p*-QM with these substituents were found to be less stable on column chromatography.

To investigate the synthetic utility of this method, de-*tert*-butylation of β-bis-arylamides was carried out (Scheme 2). Towards this, β-bis-arylamide **3a** was treated with anhydrous $AlCl_3$ in toluene, which smoothly delivered the de-*tert*-butylated compound **4a** in excellent yield (for the detailed optimized reaction conditions, see the Supporting Information). The compound **4a** represents a privileged pharmaceutically active and naturally occurring structural motif.

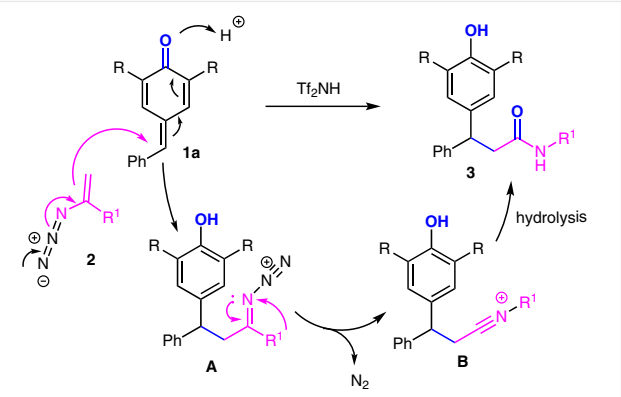


Scheme 1 Synthesis of amide from *p*-quinone methide and vinyl azide. *Reagents and conditions*: **1** (0.030–0.055 mmol), **2** (1.2 equiv), Tf_2NH (10 mol%), DCE (2 mL), r.t., 5 min. Yields refer to isolated pure products.



Scheme 2 De-*tert*-butylation of β-bis-arylamides

The plausible reaction mechanism is illustrated in Scheme 3. The *p*-QM is activated by H^+ ion (available from Brønsted acid Tf_2NH) followed by attack of vinyl azide **2**, resulting in the intermediate **A**, which undergoes Schmidt rearrangement to furnish the nitrilium ion intermediate **B**. Subsequent hydrolysis would afford the desired product **3**.



Scheme 3 Plausible mechanism for the formation of β-bis-arylamides

In summary, we have developed a method for the synthesis of β-bis-arylamides using Tf_2NH catalyzed 1,6-conjugate addition of phenyl vinyl azide with *p*-quinone methide. The optimized method is catalytic, highly efficient concerning yields, reaction time, and the broad applicability of substrate. Further studies to explore the Michael acceptor property of *p*-quinone methide with other substrate are underway in our laboratory.

TLC was carried out on silica gel 60 F245, precoated aluminum sheets, and visualized by UV lamp (254 nm) and staining with the anisaldehyde solution. Synthesized compounds were purified by column chromatography on silica gel (100–200 mesh). The chemicals, which are bought commercially, were used directly for the reaction without any purification. Melting points were measured with Buchi Melting point B-540. ^1H and ^{13}C spectra were recorded on a Bruker AV-400 and Bruker AV-500 spectrometers. Chemical shifts are reported in ppm, ^1H NMR spectra were referenced to $CDCl_3$ (7.27 ppm) and ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm). IR spectra were recorded on a Bruker ALPHA FTIR spectrometer. HRMS data were obtained via ORBITRAP mass analyzer. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

Phenylacetylene, Ag_2CO_3, DMSO, CH_2Cl_2, dichloroethane (DCE), petroleum ether (PE), EtOAc, $BF_3{\cdot}OEt_2$, and Tf_2NH were used as received from commercial suppliers. All *p*-quinone methides and aryl vinyl azides were prepared according to literature reports (see SI).

β-Bis-Arylamides; General Procedure

The *p*-quinone methide **1** (15 mg, 0.030–0.055 mmol), aryl vinyl azide **2** (1.2 equiv) in DCE (1 mL) were taken into an oven dried 5 mL reaction vial equipped with a magnetic bar. Then, triflimide (Tf_2NH, 10 mol%) dissolved in DCE (0.5 mL) was added dropwise, and the reaction mixture was stirred at r.t. for 5 min. The completion of the reaction was confirmed by TLC using 9:1 PE/EtOAc solvent system. The starting material *p*-quinone methide was completely consumed within 5 min. After the completion of the reaction, the reaction mass was concentrated under high vacuum, and the crude product was purified by column chromatography on silica gel 100–200 mesh to obtain the desired product.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*N*,3-diphenylpropanamide (3a)[16]

Yield: 13.5 mg (92%); white solid; mp 194–196 °C (Lit.[16] mp 193–194 °C); R_f = 0.32 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3635, 3283, 3196, 3071, 2958, 2921, 1653, 1599, 1547 1492, 1438, 1369, 1315, 1242, 1160, 762, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (app d, *J* = 4.6 Hz, 4 H), 7.23 (m, 5 H), 7.08 (s, 2 H), 7.07–7.02 (m, 1 H), 6.81 (s, 1 H), 5.12 (s, 1 H), 4.51 (t, *J* = 7.6 Hz, 1 H), 3.06 (d, *J* = 7.6 Hz, 2 H), 1.39 (s, 18 H).

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*N*-phenyl-3-(*p*-tolyl)propanamide (3b)[16]

Yield: 18.5 mg (86%); white solid; mp 208–210 °C (Lit.[16] mp 211–213 °C); R_f = 0.30 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3635, 3298, 2958, 1658, 1598, 1544, 1501, 1437, 1366, 1315, 1236, 1156, 1119, 1034, 758, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 4 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 7.6 Hz, 2 H), 7.08 (s, 2 H), 7.07–7.03 (m, 1 H), 6.79 (s, 1 H), 5.11 (s, 1 H), 4.46 (t, *J* = 7.6 Hz, 1 H), 3.04 (d, *J* = 7.6 Hz, 2 H), 2.32 (s, 3 H), 1.39 (s, 18 H).

3-[4-(*tert*-Butyl)phenyl]-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-phenylpropanamide (3c)

Yield: 18.6 mg (82%); colorless thick liquid; R_f = 0.33 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3636, 3299, 2957, 2926, 1658, 1597, 1550, 1437, 1368, 1316, 1241, 1119, 1035, 759, 620 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (app d, *J* = 7.9 Hz, 2 H), 7.27–7.20 (m, 4 H), 7.20–7.15 (m, 2 H), 7.11 (s, 2 H), 7.04 (t, *J* = 6.7 Hz, 1 H), 6.72 (s, 1 H), 5.12 (s, 1 H), 4.45 (t, *J* = 7.6 Hz, 1 H), 3.05 (d, *J* = 7.9 Hz, 2 H), 1.40 (s, 18 H), 1.30 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 152.5, 149.3, 140.8, 137.6, 136.1, 134.0, 128.8, 127.2, 125.6, 124.2, 124.1, 119.7, 47.5, 45.5, 34.4, 31.3, 30.3.

HRMS (FTMS + p ESI): *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{44}NO_2$: 486.3367; found: 486.3367.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(4-methoxyphenyl)-*N*-phenylpropanamide (3d)[16]

Yield: 19.5 mg (92%); white solid; mp 190–192 °C (Lit.[16] mp 191–192 °C); R_f = 0.46 (1:4 EtOAc/PE).

IR ($CHCl_3$): 3791, 3301, 2956, 2925, 1658, 1600, 1547, 1511, 1483, 1312, 1248, 1178, 1155, 1120, 1035, 756 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.18 (m, 6 H), 7.07 (s, 2 H), 7.06–7.03 (m, 1 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 6.83–6.78 (m, 1 H), 5.11 (s, 1 H), 4.46 (t, *J* = 7.6 Hz, 1 H), 3.79 (s, 3 H), 3.02 (d, *J* = 7.6 Hz, 2 H), 1.39 (s, 18 H).

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(2-methoxyphenyl)-*N*-phenylpropanamide (3e)

Yield: 18.7 mg (88%); colorless thick liquid; R_f = 0.43 (1:4 EtOAc/PE).

IR ($CHCl_3$): 3630, 3313, 2957, 2926, 1658, 1596, 1490, 1436, 1316, 1242, 1118, 1035, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.18 (m, 5 H), 7.26–7.18 (m, 1 H), 7.16 (s, 2 H), 7.08–7.01 (m, 1 H), 6.99 (s, 1 H), 6.94 (t, *J* = 7.9 Hz, 1 H), 6.88 (d, *J* = 7.9 Hz, 1 H), 5.10 (s, 1 H), 4.86 (t, *J* = 7.6 Hz, 1 H), 3.84 (s, 3 H), 3.16–3.03 (m, 2 H), 1.40 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 156.7, 152.4, 135.9, 133.4, 132.2, 128.8, 128.0, 127.6, 124.5, 124.0, 120.8, 119.6, 110.9, 55.5, 44.0, 41.1, 34.4, 30.3.

HRMS (FTMS + p ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{38}NO_3$: 460.2846; found: 460.2837.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-*N*-phenylpropanamide (3f)[16]

Yield: 18 mg (87%); colorless thick liquid; R_f = 0.6 (1:1 EtOAc/PE).

IR ($CHCl_3$): 3635, 3349, 2958, 2924, 2861, 1656, 1596, 1511, 1437, 1315, 1256, 1125, 1031, 768 cm^{-1}.

^1H NMR (500MHz, $CDCl_3$): δ = 7.25 (app d, *J* = 4.2 Hz, 4 H), 7.09 (s, 2 H), 7.07–7.02 (m, 1 H), 6.88–6.77 (m, 4 H), 5.12 (s, 1 H), 4.46 (t, *J* = 7.4 Hz, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.02 (d, *J* = 7.6 Hz, 2 H), 1.40 (s, 18 H).

3-(4-Chlorophenyl)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-phenylpropanamide (3g)

Yield: 17 mg (93%); white solid; mp 216–218 °C; R_f = 0.2 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3633, 3280, 2958, 2925, 1649, 1596, 1489, 1436, 1318, 1219, 1119, 1040, 766 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 8 H), 7.10–7.05 (m, 1 H), 7.03 (s, 2 H), 6.85 (s, 1 H), 5.14 (s, 1 H), 4.52 (t, *J* = 7.6 Hz, 1 H), 3.06–2.96 (m, 2 H), 1.39 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 152.6, 142.5, 137.5, 136.2, 133.5, 132.2, 129.0, 128.9, 128.7, 124.3, 124.1, 119.8, 46.9, 45.0, 34.4, 30.2.

HRMS (FTMS + p ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{35}ClNO_2$: 464.2351; found: 464.2351.

3-(2-Bromophenyl)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-phenylpropanamide (3h)

Yield: 20 mg (97%); white solid; mp 226–228 °C; R_f = 0.26 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3630, 3381, 3022, 2926, 2402, 1656, 1594, 1421, 1318 1216, 1121, 1037, 764 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.9 Hz, 1 H), 7.38–7.21 (m, 6 H), 7.15 (s, 2 H), 7.09–7.04 (m, 2 H), 6.95 (s, 1 H), 5.13 (s, 1 H), 5.00 (t, *J* = 7.6 Hz, 1 H), 3.09 (d, *J* = 7.9 Hz, 2 H), 1.39 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 152.6, 142.9, 137.6, 136.1, 133.4, 132.2, 128.9, 128.1, 128.0, 127.7, 124.9, 124.5, 124.2, 119.7, 46.0, 44.2, 34.4, 30.3.

HRMS (FTMS + p ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{35}BrNO_2$: 508.1846; found: 508.1847.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(4-nitrophenyl)-*N*-phenylpropanamide (3i)[16]

Yield: 17.5 mg (83%); white solid; mp 216–218 °C (mp was not in accordance with Lit.[16] mp 108–110 °C); R_f = 0.2 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3629, 3252, 3197, 3138, 2959, 2867, 1654, 1599, 1547, 1523, 1438, 1348, 1238, 1154, 1115, 759 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.29 (br s, 1 H), 7.27–7.17 (m, 3 H), 7.05 (t, *J* = 7.1 Hz, 1 H), 6.99 (s, 2 H), 6.94 (s, 1 H), 5.14 (s, 1 H), 4.66 (t, *J* = 7.4 Hz, 1 H), 3.04 (d, *J* = 7.2 Hz, 2 H), 1.35 (s, 18 H).

Methyl 4-[1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-oxo-3-(phenylamino)propyl]benzoate (3j)[16]

Yield: 18 mg (87%); white solid; mp 200–202 °C (Lit.[16] mp 197–198 °C); R_f = 0.20 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3632, 3313, 2956, 2867, 1717, 1661, 1601, 1545, 1437, 1283, 1114, 1027, 759 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.9 Hz, 2 H), 7.39 (d, *J* = 7.9 Hz, 2 H), 7.30–7.20 (m, 6 H), 7.12–7.05 (m, 1 H), 7.04 (s, 2 H), 6.90 (s, 1 H), 5.14 (s, 1 H), 4.61 (t, *J* = 7.3 Hz, 1 H), 3.90 (s, 3 H), 3.06 (d, *J* = 7.9 Hz, 2 H), 1.38 (s, 18 H).

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(naphthalen-2-yl)-*N*-phenylpropanamide (3k)[16]

Yield: 16.5 mg (81%); white solid; mp 228–230 °C (Lit.[16] mp 230–231 °C); R_f = 0.3 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3630, 3357, 3020, 2925, 2400, 1656, 1597, 1420, 1215, 1122, 1040, 758, 669 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.84–7.73 (m, 4 H), 7.51–7.40 (m, 3 H), 7.21 (app s, 4 H), 7.13 (s, 2 H), 7.08–7.00 (m, 1 H), 6.83 (s, 1 H), 5.13 (s, 1 H), 4.69 (t, *J* = 7.6 Hz, 1 H), 3.21–3.09 (m, 2 H), 1.39 (s, 18 H).

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(naphthalen-1-yl)-*N*-phenylpropanamide (3l)

Yield: 19.5 mg (94%); thick colorless liquid; R_f = 0.3 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3630, 3350, 2924, 2858, 1653, 1596, 1435, 1317, 1224, 1121, 1041, 771 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.76 (d, *J* = 7.6 Hz, 1 H), 7.51–7.43 (m, 4 H), 7.23 (app d, *J* = 4.2 Hz, 3 H), 7.15 (s, 2 H), 7.09–7.01 (m, 1 H), 6.84 (s, 1 H), 5.41–5.30 (m, 1 H), 5.09 (s, 1 H), 3.26–3.08 (m, 2 H), 1.35 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 152.4, 139.7, 137.6, 136.1, 134.1, 133.5, 131.5, 128.8, 128.8, 127.3, 126.2, 125.5, 125.3, 124.4, 124.1, 123.9, 123.9, 119.7, 45.5, 43.0, 34.3, 30.2.

HRMS (FTMS + p ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{38}NO_2$: 480.2897; found: 480.2899.

3-(Benzo[*d*][1,3]dioxol-4-yl)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-phenylpropanamide (3m)

Yield: 19.5 mg (95%); thick colorless liquid; R_f = 0.42 (1:4 EtOAc/PE).

IR ($CHCl_3$): 3633, 3289, 3139, 2959, 2922, 1657, 1600, 1544, 1492, 1438, 1365, 1314, 1242, 1158, 1118, 1039, 934, 808, 758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.23 (m, 4 H), 7.06 (s, 3 H), 6.85 (s, 1 H), 6.82–6.72 (m, 3 H), 5.92 (app d, *J* = 2.7 Hz, 2 H), 5.12 (s, 1 H), 4.44 (t, *J* = 7.6 Hz, 1 H), 3.00 (d, *J* = 8.0 Hz, 2 H), 1.40 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 152.5, 147.8, 146.1, 137.9, 137.6, 136.1, 134.1, 128.9, 124.2, 124.0, 120.5, 119.8, 108.3, 108.2, 100.9, 47.3, 45.3, 34.4, 30.3.

HRMS (FTMS + p ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{36}NO_4$: 474.2637; found: 474.2637.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*N*-phenyl-3-(thiophen-2-yl)propanamide (3n)[16]

Yield: 15.5 mg (71%); white solid; mp 170–172 °C (Lit.[16] mp 172–175 °C); R_f = 0.20 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3634, 3372, 2925, 2858, 1653, 1595, 1436, 1317, 1246, 1121, 1040, 769, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (app s, 4 H), 7.18 (app d, *J* = 4.3 Hz, 1 H), 7.15 (s, 2 H), 7.07 (br s, 1 H), 6.99–6.88 (m, 2 H), 6.82 (s, 1 H), 5.15 (s, 1 H), 4.76 (t, *J* = 7.3 Hz, 1 H), 3.13–2.95 (m, 2 H), 1.41 (s, 18 H).

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-phenyl-*N*-(*p*-tolyl)propanamide (3o)[16]

Yield: 21 mg (93%); colorless thick liquid; R_f = 0.5 (1:4 EtOAc/PE).

IR ($CHCl_3$): 3632, 3288, 2924, 2861, 1650, 1598, 1428, 1317, 1245, 1120, 1037, 816, 772 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (app d, *J* = 4.2 Hz, 4 H), 7.24–7.19 (m, 1 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 7.08 (s, 2 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 6.72 (s, 1 H), 5.11 (s, 1 H), 4.51 (t, *J* = 7.6 Hz, 1 H), 3.04 (d, *J* = 7.6 Hz, 2 H), 2.28 (s, 3 H), 1.39 (s, 18 H).

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*N*-(2-methoxyphenyl)-3-phenylpropanamide (3p)[16]

Reaction performed with *p*-quinone methide **1p** (20 mg, 0.068 mmol) and vinyl azide **2p** (1.2 equiv); yield: 27 mg (95%); colorless liquid; R_f = 0.5 (1:4 EtOAc/PE).

IR ($CHCl_3$): 3634, 3372, 2926, 2859, 1656, 1594, 1533, 1457, 1424, 1319, 1251, 1121, 1038, 857, 775 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.0 Hz, 1 H), 7.57 (s, 1 H), 7.36–7.28 (m, 4 H), 7.22–7.19 (m, 1 H), 7.06 (s, 2 H), 6.99 (t, *J* = 7.2 Hz, 1 H), 6.92 (t, *J* = 7.4 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 5.06 (s, 1 H), 4.56 (t, *J* = 7.6 Hz, 1 H), 3.76 (s, 3 H), 3.16–3.01 (m, 2 H), 1.38 (s, 18 H).

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*N*-(3,4-difluorophenyl)-3-phenylpropanamide (3q)

Yield: 20.1 mg (85%); colorless thick liquid; R_f = 0.3 (1:9 EtOAc/PE).

IR ($CHCl_3$): 3634, 3289, 2960, 2854, 1660, 1613, 1248, 1210, 1158, 1118, 1037, 910, 865, 809, 771 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 7.26–7.20 (m, 1 H), 7.07 (s, 2 H), 7.00 (q, *J* = 8.9 Hz, 1 H), 6.76–6.66 (m, 2 H), 5.13 (s, 1 H), 4.48 (t, *J* = 7.8 Hz, 1 H), 3.04 (d, *J* = 7.6 Hz, 2 H), 1.39 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.0, 152.8, 151.2, 143.9, 136.5, 134.3, 134.0, 129.0, 127.9, 126.9, 125.6, 124.4, 117.3 (d, $J_{C,F}$ = 19.1 Hz), 115.5, 109.8 (d, $J_{C,F}$ = 21.9 Hz), 48.0, 45.4, 34.7, 30.5.

HRMS (FTMS + p ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{34}F_2NO_2$: 466.2552; found: 466.2556.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*N*-hexyl-3-phenylpropanamide (3r)

Reaction performed with *p*-quinone methide **1a** (20 mg, 0.068 mmol) and vinyl azide **2e** (1.2 equiv); yield: 18 mg (75%); colorless thick liquid; R_f = 0.34 (1:5 EtOAc/PE).

IR ($CHCl_3$): 3356, 2945, 2833, 1657, 1450, 1415, 1114, 1032, 758 cm^{-1}.

^{1}H NMR (500 MHz , $CDCl_3$): δ = 7.35–7.27 (m, 4 H), 7.22–7.18 (m, 1 H), 7.05 (s, 2 H), 5.16 (br s, 1 H), 5.09 (s, 1 H), 4.44 (t, *J* = 7.8 Hz, 1 H), 3.17–3.00 (m, 2 H), 2.92–2.81 (m, 2 H), 1.41 (s, 18 H), 1.27–1.14 (m, 6 H), 1.13–1.06 (m, 2 H), 0.87 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 152.3, 144.1, 135.8, 134.2, 128.5, 127.7, 126.3, 124.2, 47.7, 44.3, 39.4, 34.4, 31.4, 30.3, 29.3, 26.3, 22.5, 14.0.

HRMS (FTMS + p ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{44}NO_2$: 438.3367; found: 438.3363.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*N*-hexyl-3-(*p*-tolyl)propanamide (3s)

Reaction performed with *p*-quinone methide **1b** (20 mg, 0.065 mmol) and vinyl azide **2e** (1.2 equiv); yield: 23 mg (79%); colorless thick liquid; R_f = 0.40 (1:5 EtOAc/PE).

IR ($CHCl_3$): 3357, 2945, 2833, 1655, 1453, 1415, 1113, 1026, 759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.13 (m, 2 H), 7.13–7.07 (m, 2 H), 7.04 (s, 2 H), 5.17 (br s, 1 H), 5.07 (s, 1 H), 4.38 (t, *J* = 7.8 Hz, 1 H), 3.16–3.00 (m, 2 H), 2.91–2.78 (m, 2 H), 2.31 (s, 3 H), 1.40 (s, 18 H), 1.26–1.15 (m, 6 H), 1.12–1.05 (m, 2 H), 0.86 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 152.2, 141.1, 135.8, 135.8, 134.4, 129.2, 127.5, 124.1, 47.4, 44.3, 39.4, 34.3, 31.4, 30.3, 29.3, 26.3, 22.4, 20.9, 14.0.

HRMS (FTMS + p ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{46}NO_2$: 452.3523; found: 452.3522.

3-(4-Hydroxy-3,5-dimethylphenyl)-*N*,3-diphenylpropanamide (3t)

Reaction performed with of *p*-quinone methide **1o** (20 mg, 0.095 mmol) and vinyl azide **2a** (1.2 equiv); yield: 20 mg (61%); colorless thick liquid; R_f = 0.38 (1:2 EtOAc/PE).

IR ($CHCl_3$): 3356, 2945, 2833, 1657, 1450, 1416, 1114, 1032, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 6 H), 7.23 (app d, *J* = 7.9 Hz, 3 H), 7.07 (br s, 1 H), 6.92 (br s, 1 H), 6.89 (s, 2 H), 4.63 (br s, 1 H), 4.50 (t, *J* = 7.6 Hz, 1 H), 3.04 (d, *J* = 7.3 Hz, 2 H), 2.20 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 150.9, 144.1, 137.5, 135.0, 128.8, 128.7, 127.8, 127.6, 126.5, 124.3, 123.3, 120.0, 46.8, 44.6, 16.0.

HRMS (FTMS + p ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{24}NO_2$: 346.1802; found: 346.1798.

***N*-Hexyl-3-(4-hydroxy-3,5-dimethylphenyl)-3-phenylpropanamide (3u)**

Yield. 14 mg (83%); colorless thick liquid; R_f = 0.45 (1:2 EtOAc/PE).

IR ($CHCl_3$): 3410, 2952, 2843, 1644, 1456, 1412, 1113, 1019 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (app d, *J* = 7.2 Hz, 2 H), 7.25–7.21 (m, 2 H), 7.20–7.15 (m, 1 H), 6.84 (s, 2 H), 5.18 (br s, 1 H), 4.60 (br s, 1 H), 4.40 (t, *J* = 7.8 Hz, 1 H), 3.17–3.02 (m, 2 H), 2.83 (d, *J* = 8.0 Hz, 2 H), 2.20 (s, 6 H), 1.29–1.13 (m, 8 H), 1.11–1.04 (m, 2 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2, 150.8, 144.3, 135.2, 128.5, 127.8, 127.6, 126.3, 123.0, 46.8, 43.8, 39.4, 31.4, 29.4, 26.3, 22.5, 16.0, 14.0.

HRMS (FTMS + p ESI): m/z [M + H]$^+$ calcd for $C_{23}H_{32}NO_2$: 354.2428; found: 354.2428.

De-*tert*-butylation of β-Bis-Arylamides; 3-(4-Hydroxyphenyl)-*N*,3-diphenylpropanamide (4a);[16] Typical Procedure

In an oven-dried 50 mL round-bottomed flask, compound **3a** (50 mg, 0.11 mmol) was taken in anhyd toluene (10 mL) followed by the addition of anhyd $AlCl_3$ (94.2 mg, 0.698 mmol) at once, under an argon atmosphere. The reaction mixture was stirred at r.t. until the completion of reaction. The mixture was cooled to 0 °C and ice water was added to quench the $AlCl_3$. The mixture was extracted with EtOAc (3 × 15 mL), the combined organic layers were dried (anhyd Na_2SO_4), and concentrated under reduced pressure followed by column chromatography purification to give **4a**; yield: 13 mg (88%); colorless thick liquid; R_f = 0.20 (1:2 EtOAc/PE).

IR ($CHCl_3$): 3356, 2945, 2832, 1657, 1453, 1416, 1114, 1029,758 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.95 (s, 1 H), 9.28 (br s, 1 H), 7.52–7.42 (m, J = 8.0 Hz, 2 H), 7.32–7.18 (m, 6 H), 7.18–7.03 (m, 3 H), 6.99 (app t, J = 7.2 Hz, 1 H), 6.71–6.60 (m, J = 8.0 Hz, 2 H), 4.45 (t, J = 8.0 Hz, 1 H), 3.01 (d, J = 8.0 Hz, 2 H).

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Supporting Information

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