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# $BF_3$·$OEt_2$-Catalyzed Synthesis of *anti*-β-(*N*-Arylamino)-α-hydroxynitriles by Regio- and Diastereospecific Ring Opening of 3-Aryloxirane-2-carbonitriles with Anilines

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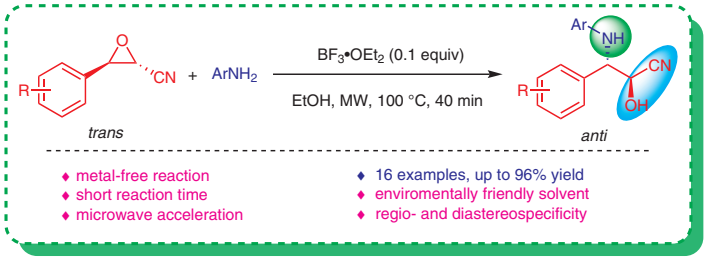


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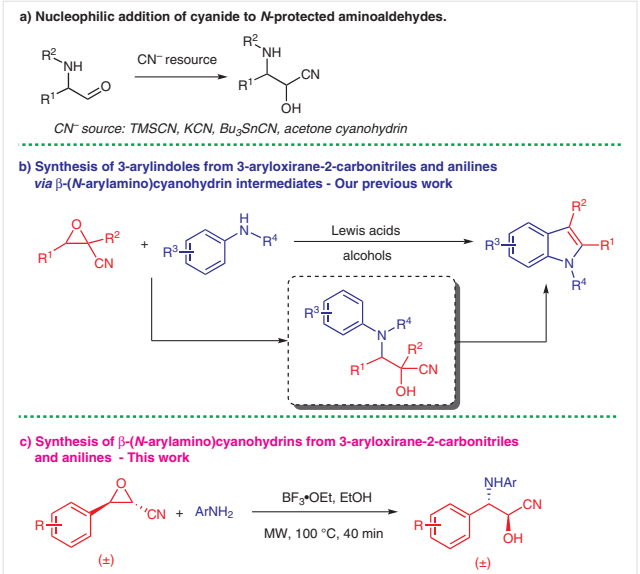
**Abstract** A safe and convenient synthetic method to *anti*-β-(*N*-arylamino)-α-hydroxynitriles from 3-aryloxirane-2-carbonitriles and anilines was developed under the catalysis of $BF_3$·$OEt_2$ in ethanol. In this method, $BF_3$·$OEt_2$ first reacts with ethanol to produce the true catalyst of super acid H[B(OEt)$F_3$], followed by an acid-catalyzed regio- and diastereospecific ring opening of oxirane-2-carbonitriles with anilines, generating *anti*-β-(*N*-arylamino)-α-hydroxynitriles. The method features the advantages of non-metal catalysis, short reaction times, and easy operation, and uses an environmentally friendly solvent.

**Key words** amino-hydroxynitrile, boron trifluoride, ring opening, regiospecificity, diastereospecificity, oxiranecarbonitrile, aniline

Considerable effort has continually been devoted to the development of new synthetic methodology in basic organic synthesis to cater for the needs of the synthesis or modification of drugs, natural products, and organic functional materials. Cyanohydrins are versatile building blocks in synthetic organic chemistry in which the two functional groups hydroxyl and cyano group connect to the same carbon nucleus, making them not only possessing the ability to participate in monofunctional group conversion reactions,[1] but also bifunctional group conversion reactions.[2–4] Furthermore, cyanohydrins are also proven to be biological active molecules[3,5,6] and have certain biological applications.[7] Traditional methods for the synthesis of cyanohydrins and their *O*-protected derivatives involved the addition of highly toxic cyanide to aldehydes or ketones.[6,8] These methods are generally dangerous to operate, and this limits their applications. To overcome these disadvantages, Orru[9] and Lian[10] achieved the synthesis of *O*-protected cyanohydrins by employing low or nontoxic trityl isocyanide and malononitriles, respectively. As a result, the development of novel, safe, and practical methods for construction of cyanohydrins still is an issue to deeply investigate.

β-Aminocyanohydrins, derivatives of cyanohydrins, are also proven to be biologically active compounds[3,5] and have prevalent applications in the synthesis of β-amino-α-hydroxycarboxylic acid derivatives[11] and heterocyclic compounds.[2,3] However, there are few investigations on the synthesis of β-aminocyanohydrins, all of which involve the addition of highly toxic cyanide sources to the corresponding *N*-protected β-aminoaldehydes (Scheme 1a).[5,11,12] More recently, we reported a new method for the synthesis of 2-arylindoles from vicinal 3-aryloxirane-2-carbonitriles and anilines, and showed that β-(*N*-arylamino)cyanohydrins are important intermediates (Scheme 1b).[2] Inspired by our previous work,[2] a microwave-assisted $BF_3$·$OEt_2$-catalyzed synthesis of *anti*-β-(*N*-arylamino)-α-hydroxynitriles through regio- and diastereospecific ring opening of ox-




**Scheme 1** Methods of synthesis of β-aminocyanohydrins

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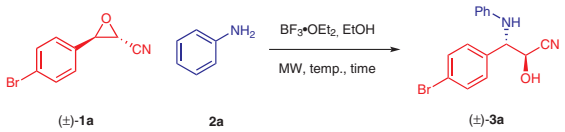
irane-2-carbonitriles with anilines in ethanol was developed (Scheme 1c). The reaction is of synthetic importance and has the advantages of short reaction times, non-metal catalysis, a cyanide-free reagent, and an environmentally friendly solvent.

**Table 1** Optimization of the Reaction Conditions[a]




(±)-**1a** **2a** (±)-**3a**

| Entry | Equiv of **2a** | Time (min) | Temp (°C) | Yield (%) of **3a** |
|---|---|---|---|---|
| 1 | 1.4 | 30 | 78 | 61 |
| 2 | 1.4 | 30 | 90 | 65 |
| 3 | 1.4 | 30 | 100 | 92 |
| 4 | 1.4 | 30 | 110 | 90 |
| 5 | 1.4 | 30 | 120 | 88 |
| 6 | 1.4 | 20 | 100 | 61 |
| **7** | **1.4** | **40** | **100** | **97 (96[b])** |
| 8 | 1.4 | 50 | 100 | 86 |
| 9 | 1.4 | 60 | 100 | 90 |
| 10[c] | 1.4 | 40 | 100 | 82 |
| 11[d] | 1.4 | 40 | 100 | 44 |
| 12 | 1.3 | 40 | 100 | 83 |
| 13 | 1.5 | 40 | 100 | 85 |

[a] Reaction conditions: **1a** (0.5 mmol), $BF_3{\cdot}OEt_2$ (0.1 equiv), commercial EtOH (3 mL), microwave irradiation, sealed vessel; yields determined by $^1H$ NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.
[b] Yield of isolated product is indicated.
[c] $BF_3{\cdot}OEt_2$ (0.2 equiv) was employed.
[d] Reaction was performed without $BF_3{\cdot}OEt_2$.

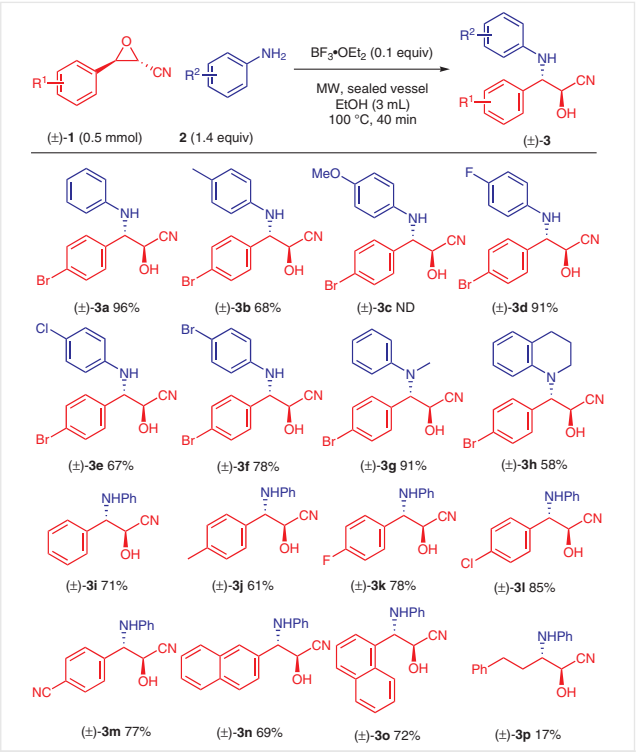
We started our studies by using *trans*-3-(4-bromophenyl)oxirane-2-carbonitrile (**1a**) and aniline (**2a**) as the model substrates. After preliminary screening of the reaction conditions with different solvents, acids, and its equivalents, loading of aniline, and reaction times [for details, see Table S1 in the Supporting Information (SI)], we found that when **1a** (0.5 mmol, 112 mg), aniline (0.7 mmol, 65 mg), and $BF_3{\cdot}OEt_2$ (0.05 mmol, 7 μL) in 5 mL of commercial ethanol were refluxed for 11 hours, *anti*-3-(4-bromophenyl)-2-hydroxy-3-(phenylamino)propanenitrile (**3a**) was obtained in the highest NMR yield of 88% [Table S1 (SI), entry 37]. To get a better yield, the reaction was performed under microwave irradiation in a sealed vessel (Table 1). Stirring **1a** (0.5 mmol, 112 mg), aniline (0.7 mmol, 65 mg), and $BF_3{\cdot}OEt_2$ (0.05 mmol, 7 μL) in 3 mL of commercial ethanol at 78 °C for 30 minutes under microwave irradiation in a sealed vessel afforded the product **3a** in 61% NMR yield (Table 1, entry 1). Furthermore, screening of the reaction temperature indicated that the reaction performed better at 100 °C, affording **3a** in 92% NMR yield (Table 1, entries 2–5). Moreover, the reaction time was also investigated. Shortening the reaction time to 20 minutes gave **3a** in a lower NMR yield of 61% (Table 1, entry 6), but prolonging the reaction time to 40 minutes gave **3a** in a higher NMR yield of 97% and 96% isolated yield (Table 1, entry 7). Further prolonging of the reaction time did not improve the yield (Table 1, entries 8 and 9). Finally, the number of equivalents of aniline and $BF_3{\cdot}OEt_2$ was adjusted slightly, however neither increasing nor decreasing them improved the yield (Table 1, entries 10–13). Overall, the best reaction conditions are **1a** (112 mg, 0.5 mmol), aniline (65 mg, 0.7 mmol), and $BF_3{\cdot}OEt_2$ (7 μL, 0.05 mmol) in 3 mL of commercial ethanol stirred at 100 °C for 40 minutes under microwave irradiation in a sealed vessel, giving the product *anti*-β-(*N*-arylamino)cyanohydrin **3a** in 96% yield.

With the established conditions in hand, the scope and generality of the reaction were investigated and the results are summarized in Scheme 2. First of all, the reactions of different of anilines with *trans*-3-(4-bromophenyl)oxirane-2-carbonitrile (**1a**) were investigated. Both electron-rich and electron-deficient anilines **2a–f** and even *N*-alkylanilines **2g** and **2h**, were well suited for the reaction and gave the corresponding products **3a–h** in satisfactory to excellent yields. For anilines with electron-donating groups, *p*-toluidine (**2b**) gave the corresponding *anti*-β-(*N*-arylamino)cyanohydrin **3b** in 68% yield. However, electron-rich 4-methoxyaniline (**2c**) could not generate the desired *anti*-β-(*N*-arylamino)cyanohydrin **3c**, but gave 2-(4-bromophenyl)-5-methoxy-1*H*-indole in 16% yield. Based on the mechanism of our previous work,[2] we thought that the formation of indole was possible due to the electron-rich aromatic ring of **3c**, making it easier to undergo an annulation process to generate the indole species. Besides, the lower yields of electron-rich anilines probably are attributed to their stronger basicity and the formation of indoles. The stronger basic anilines favor an acid-base reaction with $H[B(OEt)F_3]$ and related acids, decreasing the catalyst activity. Furthermore, halogen-substituted anilines were also tested. 4-Fluoroaniline (**2d**), 4-chloroaniline (**2e**), and 4-bromoaniline (**2f**) were suitable for the reaction, giving the desired products *anti*-β-(*N*-arylamino)cyanohydrins **3d–f** in 91%, 67%, and 78% yields, respectively. Additionally, *N*-methylaniline (**2g**) and 1,2,3,4-tetrahydroquinoline (**2h**) were also used to generate **3g** and **3h** in 91% and 58% yields. Besides, the reactions of different *trans*-3-aryloxirane-2-carbonitriles **1b–f** with aniline (**2a**) were also conducted, producing the corresponding *anti*-β-(*N*-arylamino)cyanohydrins **3i–m** in moderate to good yields. *trans*-3-Phenyloxirane-2-carbonitrile (**1b**) and *trans*-3-(*p*-tolyl)oxirane-2-carbonitrile (**1c**) gave the corresponding products **3i** and **3j** in 71% and 61% yields, respectively. In addition, halogen-substituted 3-aryloxirane-2-carbonitriles *trans*-3-(4-fluorophenyl)oxirane-2-carbonitrile (**1d**) and *trans*-3-(4-chlorophenyl)oxirane-2-carbonitrile (**1e**) generated **3k** and **3l** in 78% and 85% yields, respectively. Next, electron-deficient *trans*-3-(4-cyanophe-



nyl)oxirane-2-carbonitrile (**1f**) was investigated and gave *anti*-β-(*N*-arylamino)cyanohydrin **3m** in 77% yield. Besides, *trans*-3-(naphthalen-2-yl)oxirane-2-carbonitrile (**1g**) and *trans*-3-(naphthalen-1-yl)oxirane-2-carbonitrile (**1h**) were also examined, affording *anti*-β-(*N*-arylamino)cyanohydrins **3n** and **3o** in 69% and 72% yields, respectively. Finally, alkyl-substituted oxiranes, *anti*-3-phenethyloxirane-2-carbonitrile (**1i**) was also utilized and gave the corresponding product **3p** in 17% yield. As is described above, we can conclude that the reaction has a wide substrate scope. For electron-deficient substrates, both 3-aryloxirane-2-carbonitrile and anilines, have a little better reactivity than that of electron-rich substrates.




**Scheme 2** Scope of the reaction. *Reagents and conditions*: **1** (0.5 mmol), **2** (0.7 mmol), $BF_3{\cdot}OEt_2$ (7 μL, 0.05 mmol), commercial EtOH (3 mL), stirring, 100 °C, 40 min, microwave irradiation, sealed vessel. Yields of isolated products are indicated.

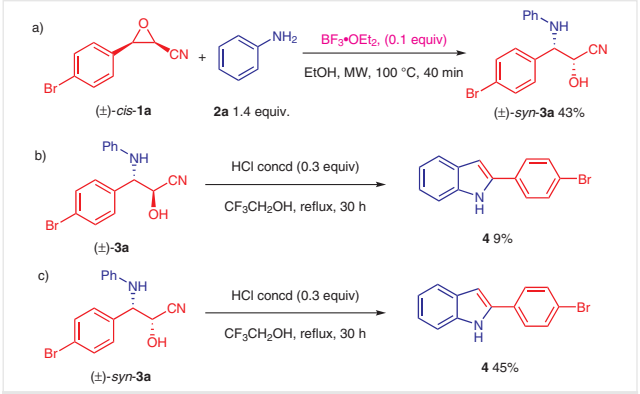
The reaction of *cis*-3-(4-bromophenyl)oxirane-2-carbonitrile (*cis*-**1a**) and aniline (**2a**) was also investigated and the corresponding product *syn*-3-(4-bromophenyl)-2-hydroxy-3-(phenylamino)propanenitrile (*syn*-**3a**) was obtained in 43% yield (Scheme 3a). The yield of *syn*-**3a** is obviously lower than that of **3a** possible due to the *cis*-cyano group, which makes the molecule more polar. The higher polarity makes *cis*-**1a** less reactive than its *trans*-isomer **1a**.

For examination of the scope of amines, we examined two representative aliphatic amines, primary amine $BnNH_2$ and secondary amine $Et_2NH$, but neither of them gave the corresponding products. That is possibly attributed to the stronger basicity of aliphatic amines than anilines, making them capture $H^+$ and lower both their reactivity and also that of the oxiranes.

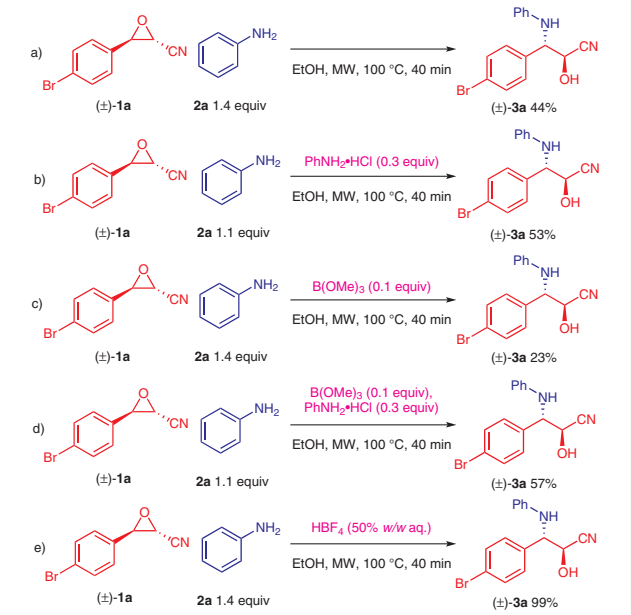
To examine the synthetic utility of the reaction, based on our previous work,[2] β-(*N*-Arylamino)cyanohydrins could be transformed into the corresponding indoles under the catalysis by concentrated HCl in refluxing 2,2,2-trifluoroethanol for 30 hours. The reactions of **3a** and *syn*-**3a** carried out under above conditions were investigated, giving the product 2-(4-bromophenyl)-1*H*-indole (**4**) in 9% and 45% yields, respectively (Scheme 3b and 3c). The results indicates that β-(*N*-arylamino)cyanohydrins have great potential application value in synthesis of indoles.

To better understand the reaction mechanism, some control experiments were taken into account (Scheme 4): the reaction of *trans*-3-(4-bromophenyl)oxirane-2-carbonitrile (**1a**) and aniline (**2a**) under the optimal conditions without $BF_3{\cdot}OEt_2$ only gave **3a** in 44% yield (Scheme 4a), the results illustrated that the use of $BF_3{\cdot}OEt_2$ is advisable for this reaction. Next, inorganic protic acid HCl (using $PhNH_2{\cdot}HCl$ as a HCl source) was utilized as the catalyst in the model reaction, producing **3a** in 53% yield, indicating proton ($H^+$) partly performed as the true catalyst (Scheme 4b). Furthermore, to examine whether trialkyl borate, which was possibly generated from the interaction between $BF_3{\cdot}OEt_2$ and alcohol, contributed to the reaction or not, $B(OMe)_3$ was employed as catalyst in the model reaction and only gave **3a** in 23% yield, lower than the reaction without catalyst (Scheme 4a). $PhNH_2{\cdot}HCl$ and $B(OMe)_3$ as co-catalysts were also investigated and gave **3a** in 57% yield, similar to the $PhNH_2{\cdot}HCl$-catalyzed reaction (Scheme 4b). The results indicates that $B(OMe)_3$ did not have any catalytic activity for this reaction (Schemes 4c and 4d). Finally, $HBF_4$ was examined and gave the product in 99% yield (Scheme 4e), which indicated that $H[B(OEt)F_3]$ might be the true catalyst in the reaction.

In our previous work,[2] 3-aryloxirane-2-carbonitriles reacted with anilines under the catalysis of $BF_3{\cdot}OEt_2$ (0.16

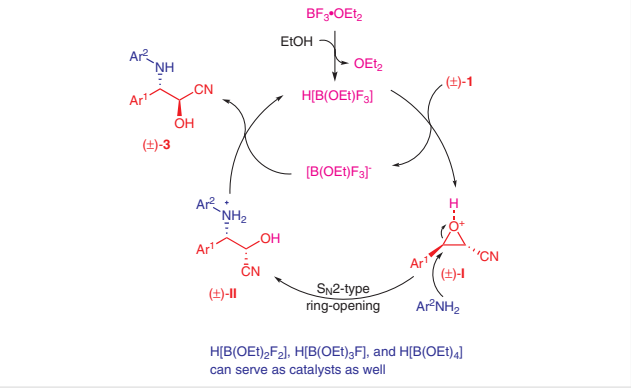



**Scheme 3** Applications of the reaction




**Scheme 4** Control experiments

equiv) or $AlCl_3$ (0.10 equiv) in the presence of 2,2,2-trifluoroethanol, producing indoles. On the basis of the control experiments and previously reported work,[2] a plausible mechanism is proposed (Scheme 5). First, $BF_3{\cdot}OEt_2$ reacts with the solvent ethanol to generate the true catalyst of $H[B(OEt)F_3]$, which subsequently reacts with ethanol to yield $H[B(OEt)_2F_2]$, $H[B(OEt)_3F]$, and $H[B(OEt)_4]$ acidic species as catalysts. $H[B(OEt)_nF_{4-n}]$ (n = 1 to 4) species activate epoxides **1** via protonation, forming intermediates **I**. Next, intermediates **I** undergo a regio- and diastereospecific $S_N2$-type ring opening of oxirane-2-carbonitriles with anilines **2**, generating intermediates **II**. The ring opening of protonated aryloxiranes regiospecifically occurs on their benzylic carbon atoms.[13] Finally, intermediates **II** give the product *anti*-β-(*N*-arylamino)cyanohydrins **3** after proton transfer to $H[B(OEt)_2F_2]^-$, regenerating the catalysts for the next catalytic cycle.




**Scheme 5** Proposed mechanism

In our previous work,[2] β-(*N*-arylamino)cyanohydrins could further generate the corresponding indole compounds catalyzed by proton acid, which is possibility caused by the stronger acidity of trifluoroethanol than ethanol. Thus, trifluoroethanol has stronger reactivity with $BF_3{\cdot}OEt_2$ and generates stronger proton acid $H[B(OCH_2CF_3)F_3]$, which not only could accelerate the regio- and diastereospecific $S_N2$-type ring-opening process, but also promote the intramolecular aromatic electrophilic substitution process, giving the products of indoles.

In summary, a microwave-assisted $BF_3{\cdot}OEt_2$-catalyzed synthesis of *anti*-β-(*N*-arylamino)cyanohydrins from 3-aryloxirane-2-carbonitriles and anilines in ethanol was developed. In this reaction, $BF_3{\cdot}OEt_2$ firstly reacts with the solvent ethanol to produce the true catalysts, super acids $H[B(OEt)_nF_{4-n}]$ (n = 1 to 4). Then an acid-catalyzed $S_N2$-type regio- and diastereospecific ring opening of 3-aryloxirane-2-carbonitriles with anilines occurs in the presence of $H[B(OEt)_nF_{4-n}]$. The reaction employed 3-aryloxirane-2-carbonitriles readily accessible from aromatic aldehydes and 2-chloroacetonitrile by Darzens reaction and anilines as the starting materials, avoiding the use of highly toxic cyanide reagents, making the reaction safe. As a result, the reaction features advantages of readily accessible starting materials, non-metal catalysis, short reaction times, cyanide-free reagents, and an environmentally friendly solvent.

Unless otherwise noted, all materials were purchased from commercial sources, and commercially available reagents were used without further purification. All reactions were performed under microwave irradiation in a sealed vessel using a CEM Discover microwave reactor. Column chromatography was carried out on silica gel (200–300 mesh) from Branch of Qingdao Haiyang Chemical Industry. Petroleum ether (PE) used for column chromatography was bp 60–90 °C. Reactions were monitored by TLC on silica gel GF254 coated 0.2-mm plates from the Institute of Yantai Chemical Industry. The plates were visualized under UV light. Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. $^1H$, $^{13}C$, and $^{19}F$ NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer in $CDCl_3$ and DMSO-$d_6$ with TMS as an internal standard. IR spectra (KBr pellets) were taken on a Nicolet 5700 FT-IR spectrophotometer. HRMS were obtained under ESI ionization using an agilent LC/MSD TOF mass spectrometer.

### β-(*N*-Arylamino)cyanohydrins 3; General Procedure

A solution of 3-aryloxirane-2-carbonitrile **1** (0.5 mmol), aniline (0.7 mmol), and $BF_3{\cdot}OEt_2$ (7 μL, 0.05 mmol) in commercial EtOH (3 mL) was stirred at 100 °C for 40 min under microwave irradiation in a sealed vessel. The mixture was cooled to r.t., and then the solution was transferred into a 25-mL flask and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, PE/EtOAc 10:1) to afford the corresponding β-(*N*-arylamino)cyanohydrins **3**.

### *anti*-3-(4-Bromophenyl)-2-hydroxy-3-(phenylamino)propanenitrile (3a)

Colorless oil; yield: 153 mg (96%); $R_f$ = 0.21 (33% EtOAc/PE).

IR (KBr): 1010, 1072, 1385, 1405, 1436, 1501, 1602, 2246, 3385 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.17 (t, *J* = 8.0 Hz, 2 H), 6.82 (t, *J* = 7.4 Hz, 1 H), 6.66 (d, *J* = 8.0 Hz, 2 H), 4.78 (d, *J* = 6.4 Hz, 1 H), 4.77 (dd, *J* = 8.0, 6.4 Hz, 1 H), 4.45 (s, 1 H), 3.17 (d, *J* = 8.0 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 145.3, 134.8, 132.4, 129.5, 128.7, 123.0, 120.0, 117.2, 114.8, 65.8, 60.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}BrN_2O$: 317.0284; found: 317.0280.

### *syn*-3-(4-Bromophenyl)-2-hydroxy-3-(phenylamino)propanenitrile (*syn*-3a)[2]

Colorless oil; yield: 68 mg (43%); $R_f$ = 0.21 (33% EtOAc/PE).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 7.15 (t, *J* = 7.8 Hz, 2 H), 6.79 (t, *J* = 7.2 Hz, 1 H), 6.61 (d, *J* = 8.0 Hz, 2 H), 4.67 (d, *J* = 6.0 Hz, 1 H), 4.64 (d, *J* = 6.0 Hz, 1 H), 4.11 (br s, 2 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 145.3, 135.7, 132.3, 129.4, 129.1, 123.0, 119.5, 117.8, 114.6, 65.1, 60.6.

### *anti*-3-(4-Bromophenyl)-2-hydroxy-3-(*p*-tolylamino)propanenitrile (3b)

Yellowish oil; yield: 112 mg (68%); $R_f$ = 0.35 (33% EtOAc/PE).

IR (KBr): 1010, 1071, 1268, 1299, 1487, 1518, 1617, 2246, 3385 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 6.58 (d, *J* = 8.4 Hz, 2 H), 4.73 (d, *J* = 4.0 Hz, 1 H), 4.72 (d, *J* = 4.0 Hz, 1 H), 4.34 (s, 1 H), 3.43 (s, 1 H), 2.23 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 142.9, 134.9, 132.3, 130.0, 129.4, 128.7, 122.9, 117.4, 115.1, 65.7, 60.7, 20.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}BrN_2O$: 331.0441; found: 331.0437.

### *anti*-3-(4-Bromophenyl)-2-hydroxy-3-[(4-methoxyphenyl)amino]propanenitrile (3c)

Not detected, but 16% of 2-(4-bromophenyl)-5-methoxy-1*H*-indole was obtained.[2]

### *anti*-3-(4-Bromophenyl)-3-[(4-fluorophenyl)amino]-2-hydroxypropanenitrile (3d)

Yellowish oil; yield: 152 mg (91%); $R_f$ = 0.38 (33% EtOAc/PE).

IR (KBr): 1011, 1072, 1221, 1406, 1488, 1510, 1604, 2250, 3386 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 6.88–6.83 (m, 2 H), 6.61–6.55 (m, 2 H), 4.73 (d, *J* = 4.0 Hz, 1 H), 4.67 (d, *J* = 4.0 Hz, 1 H), 4.41 (s, 1 H), 3.46 (s, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 157.0 (d, $J_{C\text{-}F}$ = 239.4 Hz), 141.57 (d, $J_{C\text{-}F}$ = 3.0 Hz), 134.7, 132.4, 128.7, 123.0, 117.3, 116.1 (d, $J_{C\text{-}F}$ = 2.0 Hz), 115.9 (d, $J_{C\text{-}F}$ = 13.1 Hz), 65.7, 61.1.

$^{19}F$ NMR (377 MHz, $CDCl_3$): δ = –124.52.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}BrFN_2O$: 335.0190; found: 335.0184.

### *anti*-3-(4-Bromophenyl)-3-[(4-chlorophenyl)amino]-2-hydroxypropanenitrile (3e)

The residue was subjected to silica gel column chromatography (PE/EtOAc 15:1) to give the desired product as a yellowish oil; yield: 118 mg (67%); $R_f$ = 0.40 (33% EtOAc/PE).

IR (KBr): 1011, 1072, 1180, 1271, 1294, 1313, 1406, 1494, 1600, 2252, 3385 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.8 Hz, 2 H), 6.53 (d, *J* = 8.8 Hz, 2 H), 4.72 (s, 1 H), 4.67 (s, 1 H), 4.53 (s, 1 H), 3.38 (s, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 144.0, 134.4, 132.4, 129.3, 128.7, 124.5, 123.1, 117.2, 115.9, 65.6, 60.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}BrClN_2O$: 350.9894; found: 350.9897.

### *anti*-3-(4-Bromophenyl)-3-[(4-bromophenyl)amino]-2-hydroxypropanenitrile (3f)

The residue was subjected to silica gel column chromatography (PE/EtOAc 15:1) to give the desired product as a colorless solid; yield: 154 mg (78%); mp 140–142 °C; $R_f$ = 0.34 (33% EtOAc/PE).

IR (KBr): 1011, 1073, 1313, 1405, 1491, 1594, 2251, 3388 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 7.53 (d, *J* = 8.4 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 8.8 Hz, 2 H), 6.78 (d, *J* = 6.4 Hz, 1 H), 6.60 (d, *J* = 8.8 Hz, 2 H), 6.56 (d, *J* = 8.4 Hz, 1 H), 4.74–4.66 (m, 2 H).

$^{13}C$ NMR (101 MHz, DMSO-$d_6$): δ = 146.0, 138.2, 131.4, 131.0, 130.2, 120.9, 120.0, 115.4, 107.7, 63.9, 58.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}Br_2N_2O$: 394.9389; found: 394.9393.

### *anti*-3-(4-Bromophenyl)-2-hydroxy-3-[methyl(phenyl)amino]propanenitrile (3g)

Colorless oil; yield: 150 mg (91%); $R_f$ = 0.46 (33% EtOAc/PE).

IR (KBr): 1011, 1074, 1142, 1181, 1384, 1402, 1450, 1501, 1598, 2246, 3406 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.0 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.97 (d, *J* = 8.0 Hz, 2 H), 6.92 (t, *J* = 7.6 Hz, 1 H), 5.19 (d, *J* = 6.8 Hz, 1 H), 5.07 (t, *J* = 6.4 Hz, 1 H), 3.10 (d, *J* = 7.6 Hz, 1 H), 2.78 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 150.1, 133.6, 132.0, 129.5, 129.2, 122.5, 120.0, 118.9, 115.5, 65.9, 62.0, 34.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}BrN_2O$: 331.0441; found: 661.0438.

### *anti*-3-(4-Bromophenyl)-3-[3,4-dihydroquinolin-1(2*H*)-yl]-2-hydroxypropanenitrile (3h)

Colorless oil; yield: 103 mg (58%); $R_f$ = 0.46 (33% EtOAc/PE).

IR (KBr): 1010, 1073, 1192, 1307, 1345, 1400, 1455, 1494, 1601, 2249, 3418 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.09 (t, *J* = 7.8 Hz, 1 H), 7.02 (d, *J* = 7.2 Hz, 1 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 6.72 (t, *J* = 7.2 Hz, 1 H), 5.33 (d, *J* = 6.4 Hz, 1 H), 5.13 (t, *J* = 7.0 Hz, 1 H), 3.33 (ddd, *J* = 11.2, 7.6, 2.8 Hz, 1 H), 3.15 (ddd, *J* = 11.2, 7.6, 3.2 Hz, 1 H), 2.96 (d, *J* = 8.0 Hz, 1 H), 2.77 (d, *J* = 6.0 Hz, 1 H), 2.76 (d, *J* = 6.4 Hz, 1 H), 1.96–1.87 (m, 1 H), 1.78–1.69 (m, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 144.8, 134.2, 132.1, 130.0, 129.4, 127.4, 124.2, 122.5, 118.7, 118.1, 112.0, 63.0, 61.9, 44.8, 28.0, 21.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}BrN_2O$: 357.0597; found: 357.0591.

***anti*-2-Hydroxy-3-phenyl-3-(phenylamino)propanenitrile (3i)**

The residue was subjected to silica gel column chromatography (PE/EtOAc 15:1) to give the desired product as a colorless solid; yield: 85 mg (71%); mp 98–100 °C; $R_f$ = 0.44 (33% EtOAc/PE).

IR (KBr): 1030, 1075, 1182, 1274, 1315, 1435, 1454, 1501, 1603, 2248, 3387 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.43–7.33 (m, 5 H), 7.17 (dt, *J* = 7.6, 0.8 Hz, 2 H), 6.81 (t, *J* = 7.2 Hz, 1 H), 6.70 (d, *J* = 7.6 Hz, 2 H), 4.84 (dd, *J* = 7.2, 3.6 Hz, 1 H), 4.77 (dd, *J* = 8.4, 3.6 Hz, 1 H), 4.48 (d, *J* = 7.2 Hz, 1 H), 3.29 (d, *J* = 8.8 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 145.7, 135.6, 129.4, 129.2, 128.9, 126.9, 119.8, 117.5, 114.9, 66.1, 61.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2O$: 239.1179; found: 239.1179.

***anti*-2-Hydroxy-3-(phenylamino)-3-(*p*-tolyl)propanenitrile (3j)**

The residue was subjected to silica gel column chromatography (PE/EtOAc 15:1) to give the desired product as a colorless oil; yield: 77 mg (61%); $R_f$ = 0.45 (33% EtOAc/PE).

IR (KBr): 1071, 1181, 1273, 1315, 1380, 1436, 1504, 1603, 2247, 3387 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.17 (t, *J* = 8.0 Hz, 2 H), 6.80 (t, *J* = 7.6 Hz, 1 H), 6.70 (d, *J* = 7.6 Hz, 2 H), 4.81 (s, 1 H), 4.74 (d, *J* = 4.0 Hz, 1 H), 4.45 (s, 1 H), 3.27 (s, 1 H), 2.34 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 145.8, 138.8, 132.5, 129.9, 129.4, 126.8, 119.7, 117.6, 114.9, 66.2, 60.7, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2O$: 253.1335; found: 253.1336.

***anti*-3-(4-Fluorophenyl)-2-hydroxy-3-(phenylamino)propanenitrile (3k)**

Colorless oil; yield: 100 mg (78%); $R_f$ = 0.33 (33% EtOAc/PE).

IR (KBr): 1071, 1158, 1225, 1314, 1436, 1509, 1603, 2248, 3396 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.41–7.37 (m, 2 H), 7.18 (t, *J* = 7.6 Hz, 2 H), 7.08 (t, *J* = 7.6 Hz, 2 H), 6.82 (t, *J* = 7.2 Hz, 1 H), 6.66 (d, *J* = 7.8 Hz, 2 H), 4.79 (s, 1 H), 4.73 (d, *J* = 4.0 Hz, 1 H), 4.49 (s, 1 H), 3.46 (d, *J* = 1.8 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 162.8 (d, $J_{C-F}$ = 249.5 Hz), 145.5, 131.5 (d, $J_{C-F}$ = 3.0 Hz), 129.4, 128.8 (d, $J_{C-F}$ = 8.1 Hz), 119.8, 117.5, 116.2 (d, $J_{C-F}$ = 22.2 Hz), 114.8, 65.9, 60.2.

$^{19}F$ NMR (377 MHz, $CDCl_3$): δ = –112.64.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}FN_2O$: 257.1085; found: 257.1084.

***anti*-3-(4-Chlorophenyl)-2-hydroxy-3-(phenylamino)propanenitrile (3l)**

Colorless oil; yield: 116 mg (85%); $R_f$ = 0.33 (33% EtOAc/PE).

IR (KBr): 1014, 1073, 1092, 1271, 1315, 1408, 1435, 1495, 1603, 2248, 3388 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.39–7.34 (m, 4 H), 7.17 (t, *J* = 7.6 Hz, 2 H), 6.81 (t, *J* = 7.2 Hz, 1 H), 6.66 (d, *J* = 7.6 Hz, 2 H), 4.80 (dd, *J* = 8.0, 3.6 Hz, 1 H), 4.75 (s, 1 H), 4.46 (d, *J* = 8.0 Hz, 1 H), 3.28 (s, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 145.4, 134.8, 134.2, 129.5, 129.4, 128.4, 119.9, 117.3, 114.8, 65.8, 60.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}ClN_2O$: 273.0789; found: 273.0786.

***anti*-4-[2-Cyano-2-hydroxy-1-(phenylamino)ethyl]benzonitrile (3m)**

The residue was subjected to silica gel column chromatography (PE/EtOAc 6:1) to give the desired product as a yellowish oil; yield: 101 mg (77%); $R_f$ = 0.22 (33% EtOAc/PE).

IR (KBr): 1074, 1272, 1314, 1413, 1436, 1503, 1603, 2232, 3380 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.16 (t, *J* = 8.0 Hz, 2 H), 6.81 (t, *J* = 7.6 Hz, 1 H), 6.61 (d, *J* = 8.0 Hz, 2 H), 4.83 (d, *J* = 4.0 Hz, 1 H), 4.81 (d, *J* = 4.0 Hz, 1 H), 4.60 (s, 1 H), 3.62 (s, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 145.1, 141.8, 132.8, 129.5, 128.2, 119.8, 118.3, 117.1, 114.5, 112.4, 65.1, 60.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}N_3O$: 264.1131; found: 264.1139.

***anti*-2-Hydroxy-3-(naphthalen-2-yl)-3-(phenylamino)propanenitrile (3n)**

The residue was subjected to silica gel column chromatography (PE/EtOAc 15:1) to give the desired product as a colorless oil; yield: 77 mg (69%); $R_f$ = 0.37 (33% EtOAc/PE).

IR (KBr): 1072, 1129, 1273, 1314, 1374, 1435, 1504, 1602, 2247, 3388 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.8 Hz, 2 H), 7.84 (d, *J* = 6.4 Hz, 1 H), 7.83 (d, *J* = 6.0 Hz, 1 H), 7.52–7.50 (m, 3 H), 7.16 (t, *J* = 8.0 Hz, 2 H), 6.80 (t, *J* = 7.6 Hz, 1 H), 6.73 (d, *J* = 7.6 Hz, 2 H), 4.96 (d, *J* = 4.0 Hz, 1 H), 4.82 (d, *J* = 4.0 Hz, 1 H), 4.62 (s, 1 H), 3.49 (s, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 145.8, 133.4, 133.2, 133.2, 129.4, 129.1, 128.1, 127.7, 126.6, 126.4, 124.3, 119.6, 117.6, 114.8, 66.0, 61.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2O$: 289.1335; found: 289.1336.

***anti*-2-Hydroxy-3-(naphthalen-1-yl)-3-(phenylamino)propanenitrile (3o)**

The residue was subjected to silica gel column chromatography (PE/EtOAc 15:1) to give the desired product as a colorless solid; yield: 104 mg (72%); mp 147–149 °C; $R_f$ = 0.43 (33% EtOAc/PE).

IR (KBr): 1065, 1167, 1269, 1314, 1383, 1435, 1503, 1602, 2248, 3387 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.8 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.68–7.63 (m, 2 H), 7.57 (dt, *J* = 8.0, 0.8 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.14 (t, *J* = 8.0 Hz, 2 H), 6.79 (t, *J* = 7.4 Hz, 1 H), 6.72 (d, *J* = 7.6 Hz, 2 H), 5.68 (dd, *J* = 9.6, 3.6 Hz, 1 H), 4.96 (dd, *J* = 9.6, 3.6 Hz, 1 H), 4.66 (d, *J* = 9.2 Hz, 1 H), 3.50 (d, *J* = 10.0 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 145.5, 134.1, 130.6, 130.5, 129.7, 129.5, 129.5, 127.2, 126.1, 125.7, 124.2, 121.1, 120.0, 117.3, 115.1, 65.8, 57.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2O$: 289.1335; found: 289.1334.

***anti*-2-Hydroxy-5-phenyl-3-(phenylamino)pentanenitrile (3p)**

Colorless oil; yield: 29 mg (17%); $R_f$ = 0.47 (33% EtOAc/PE).

IR (KBr): 694, 750, 1075, 1316, 1498, 1510, 1601, 2251, 2854, 2925, 3394 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2 H), 7.22–7.18 (m, 3 H), 7.09 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.83 (t, *J* = 7.6 Hz, 1 H), 6.67 (dd, *J* = 8.4, 0.8 Hz, 2 H), 4.54 (s, 1 H), 3.69 (td, *J* = 6.8, 4.2 Hz, 1 H), 3.13 (d, *J* = 7.2 Hz, 1 H), 2.78 (dt, *J* = 14.0, 7.2 Hz, 1 H), 2.69 (dt, *J* = 14.0, 8.0 Hz, 1 H), 2.03 (q, *J* = 7.2 Hz, 2 H), 1.59 (s, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 146.7, 140.2, 129.6, 128.6, 128.4, 126.4, 119.7, 118.2, 114.5, 64.4, 56.9, 33.4, 32.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_2O$: 267.1492; found: 267.1490.

**2-(4-Bromophenyl)-1*H*-indole (4)**[2]

A solution of 3-(4-bromophenyl)-2-hydroxy-3-(phenylamino)propanenitrile **3a** or *syn*-**3a** (159 mg, 0.5 mmol) and concd HCl (12.5 μL, 0.15 mmol) in commercial 2,2,2-trifluoroethanol (5 mL) was refluxed for 30 h under open-air conditions. The mixture was cooled to r.t., and then the crude solution was quenched with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, PE/EtOAc 30:1) to afford 2-(4-bromophenyl)-1*H*-indole (**4**)[2] as a beige solid; yield: 12 mg (9% from **3a**); 61 mg (45% from *syn*-**3a**).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.23–7.19 (m, 1 H), 7.15–7.11 (m, 1 H), 6.82 (s, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 136.9, 136.67, 132.2, 131.3, 129.2, 126.6, 122.7, 121.5, 120.8, 120.5, 110.9, 100.5.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690243.

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