Three-Component Mannich Couplings En Route to Substituted Aminophenol and Benzoxazine Derivatives

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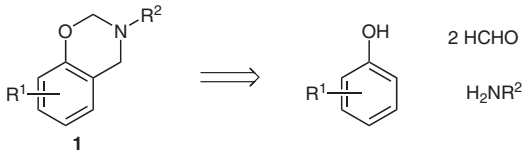
Abstract: The three-component Mannich coupling of phenols, primary amines, and aldehydes was investigated. Unexpectedly, benzoxazine products were obtained in most cases, even in instances where steric hindrance would seem to militate against benzoxazine formation. The stereoselective synthesis of such benzoxazines, their hydrolysis to aminophenol derivatives, and the mechanisms involved are presented and discussed.

Key words: benzoxazines, phenols, aldehydes, multicomponent reaction, Mannich bases

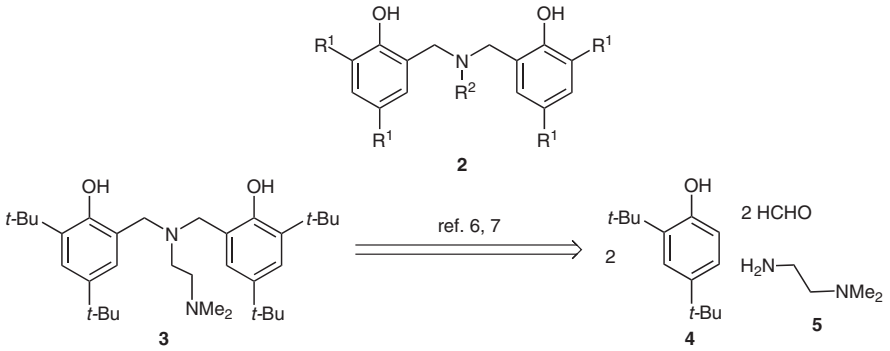
Benzoxazines are well-known compounds in the literature of the general formula **1** (Scheme 1).[1] They formally derive from the Mannich condensation of two molecules of formaldehyde with a molecule each of a phenol derivative and an amine.[2] Although the most important field of application of benzoxazine derivatives is polymer chemistry (as monomers for the production of so-called polybenzoxazine resins),[3] these compounds also exhibit a wide range of biological activities.[4] In addition, they are valuable synthetic intermediates and even hold promise for application as ionophores.[5]



Scheme 1 General structure of benzoxazine derivatives

Our interest in applications of amino(bisphenol) derivatives **2** (Scheme 2) as polydentate ligands for low-valent, early transition metals[6] led us to investigate the preparation of substituted analogues through three-component Mannich couplings. In particular, we targeted structures bearing a plethora of different side chains connected to the nitrogen atom. We[6] and others[7] have previously prepared and investigated the derivative **3** bearing an ethyl(dimethylamino) arm, through a straightforward condensation of 2,4-di-*tert*-butyl phenol **4**, formaldehyde, and the corresponding amine **5** (in the 'logical' stoichiometric 2:2:1 ratio). Surprisingly, extension of this method to other primary amine precursors **6a–c** did not afford analogous products, but instead generated the corresponding benzoxazines **7a–c** (Scheme 3).[8] Particularly, high yields of benzoxazine product were obtained with the bulky cyclohexylamine (**7b**) and adamantylamine (**7c**), thus suggesting a correlation with steric environment around the amino group.

We were intrigued by this apparent structural effect on the reaction outcome and speculated whether the use of aldehydes bulkier than formaldehyde could reroute benzoxazine formation. In contrast to our expectations, the combination of benzylamine **6a**, benzaldehyde, and phenol **4** led only to benzoxazine **7d** in nearly quantitative yield (Scheme 3, vide infra for the stereochemical assign-



Scheme 2 Standard synthetic approach to amino(bisphenol) ligands

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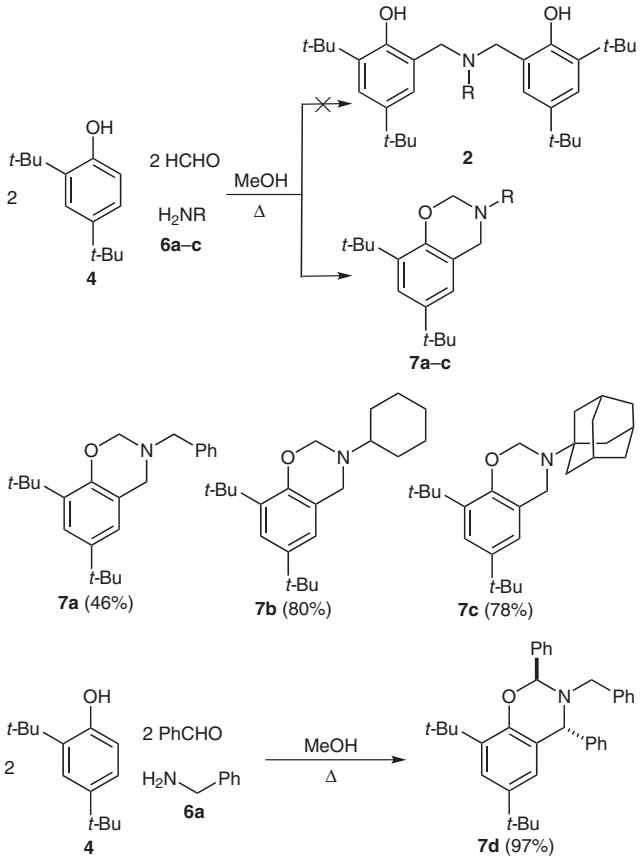
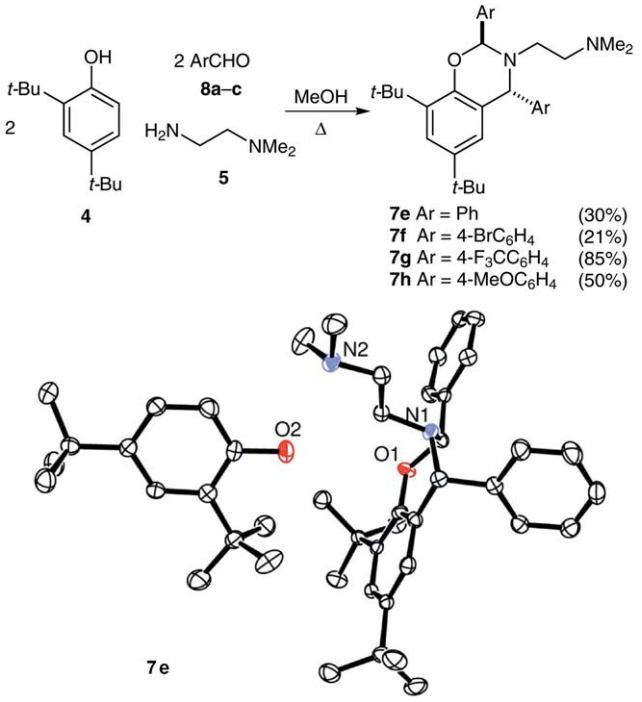


Scheme 3 Unexpected formation of benzoxazines **7a–d**

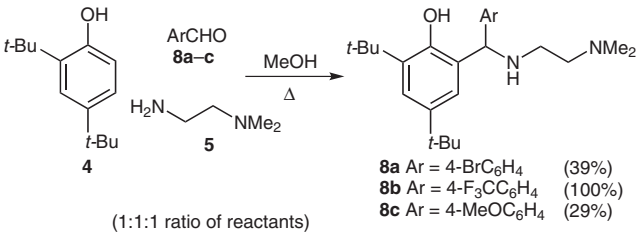
ment of **7d**).[9] This result is particularly noteworthy taking into account that benzoxazines derived from aldehydes other than formaldehyde are unusual compounds,[10] since it is assumed that steric hindrance both in the phenol component and the amine derivative significantly destabilise their formation. Indeed, when cyclohexylamine and adamantylamine were employed, benzoxazine formation was reduced (and eventually suppressed), although variable amounts of Schiff bases and amino(monophenol) derivatives were obtained (not shown).

We then decided to reevaluate *N*,*N*-dimethyl ethylenediamine **5** and examine the outcome of reactions with a variety of substituted aldehydes. Interestingly (Scheme 4), electron-rich, electron-poor, or electron-neutral aldehydes all led to the formation of the corresponding substituted benzoxazines **7e–h**[11] in moderate to excellent isolated yields. In the case of benzoxazine **7e**, crystals suitable for X-ray analysis were grown, and the structure was unambiguously determined.[12] As can be seen from Scheme 4, this confirms that the substituted benzoxazines prepared herein are selectively obtained as the *trans*-isomers. It is also interesting to note that **7e** co-crystallises with a hydrogen-bonded molecule of phenol **4**.

Since it is known that the product distribution in Mannich condensations is condition-dependent,[13] we also performed these reactions employing a 1:1:1 ratio of reactants. Strikingly (Scheme 5), little to no benzoxazine



Scheme 4 Stereoselective synthesis of substituted benzoxazines **7e–h**

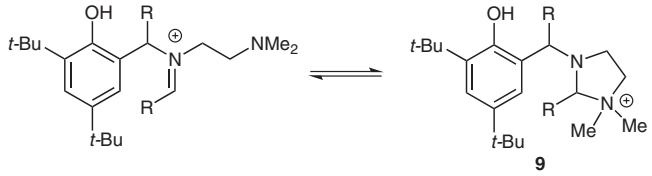


Scheme 5 Switching to the synthesis of aminophenol derivatives **8a–c** through control of stoichiometry

product was formed under such conditions and only the aminophenols **8a–c**[14] could be detected, in yields comparable to those obtained for the analogous benzoxazines **7f–h**.

It is not entirely clear at this stage why most of these reactions afford the benzoxazine product. Since it is generally accepted that steric hindrance (in a broad sense) tends to disfavour benzoxazine formation,[2,4,10] we were surprised to observe the exclusive generation of compounds **7a–h**. In these cases it may well be that the bulky substituents on the amine and the aldehyde moieties contribute to benzoxazine formation, by actually favouring those conformations of the intermediate which approach the Bürgi–Dunitz trajectory angle[15] between the phenol OH and the incipient iminium electrophile. Indeed it is apparent that, in the cases reported herein, benzoxazine formation somehow represents an energy minimum whenever excess aldehyde is present, since the resubmission of isolated benzoxazines to the reaction conditions in the presence of excess phenol did not lead to any new products even after several days of reaction.

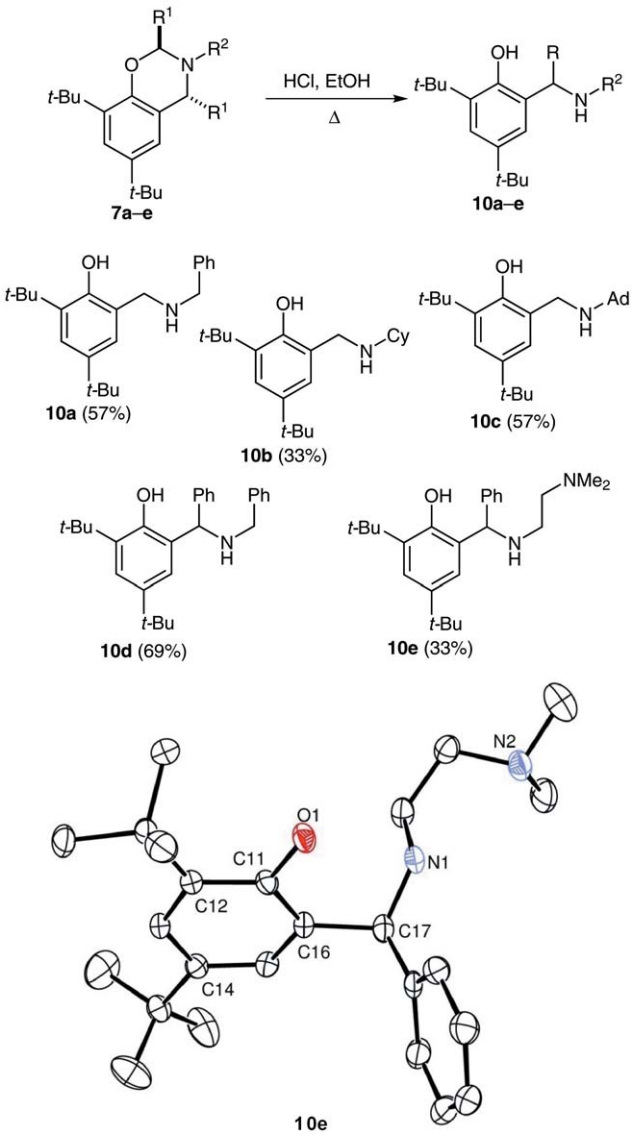
Concerning the results obtained with the *N*,*N*-dimethylamino-capped side chain, it is tempting to speculate that this substituent might allow additional, covalent stabilisation of iminium intermediates as cyclic quaternary ammonium salts **9** (Scheme 6). Such a stabilisation might effectively hamper intermolecular Mannich reaction with a second molecule of phenol, thus leading only to the observed aminophenol adducts or – in the presence of excess aldehyde – benzoxazines.



Scheme 6 Possible stabilisation 9 of iminium intermediates en route to benzoxazine formation

Finally, benzoxazine products could be uneventfully ring-opened to their aminophenol counterparts[16] under strong acidic conditions, as shown in Scheme 7. It should be further noted that, as might be anticipated from the foregoing discussion, treatment of these amino(monophenols) with varying amounts of an aldehyde (e.g., formaldehyde or benzaldehyde) and excess phenol **4** led only to the reformation of the corresponding benzoxazines.

In conclusion, we have reported the synthesis of an array of substituted benzoxazine and aminophenol compounds through very simple one-pot combination of a phenol, a primary amine, and an aldehyde. Intriguingly, the benzoxazines are obtained as the only reaction products under conditions which otherwise afforded amino(bisphenol)products in the case of formaldehyde, showcasing a dramatic steric effect in this reaction. The stereoselective obtention of such benzoxazines (isolated exclusively as the *trans*-configured isomers) may pave the way for further applications of this family of compounds in polymer science and crop research.



Scheme 7 Ring opening of benzoxazines **7a–e**; Ad = adamantyl, Cy = cyclohexyl

General Procedure for Substituted 3,4-Dihydro-2*H*-1,3-benzoxazines

A solution of 2,4-di-*tert*-butylphenol (12.1 mmol), primary amine (12 mmol), and aldehyde (33 mmol) in MeOH (10 mL) was refluxed overnight. The mixture was cooled to –20 °C, and the precipitate formed was filtered and washed thoroughly with ice-cold MeOH to give the product as a white powder, which was purified by recrystallization from MeOH.

General Procedure for Ring Opening of 3,4-Dihydro-2*H*-1,3-benzoxazines

To a solution of the benzoxazine (4.1 mmol) in EtOH (ca. 25 mL) was added HCl aq 37% until pH <1. The mixture was heated during 2 h and then evaporated to dryness. Et_2O was added until a precipitate appeared. The precipitate was filtered and dissolved in H_2O (in some cases addition of EtOH was required to dissolve the precipitate). The pH of the solution was neutralised to 7 with an aqueous solution of K_2CO_3. The precipitate obtained was filtered and dried.

Acknowledgment

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(8) Compound **7a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (m, 5 H, Ar), 7.07 (d, J_{HH} = 2.08 Hz, 1 H, Ar), 6.67 (d, J_{HH} = 2.21 Hz, 1 H, Ar), 4.71 (s, 2 H, NCH_2O), 3.90 (s, 2 H, $ArCH_2N$), 3.80 (s, 2 H, CH_2Ph), 1.30 [s, 9 H, $C(CH_3)_3$], 1.70 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C-{^{1}H} NMR (75 MHz , $CDCl_3$): δ = 150.7, 142.2, 138.5, 136.7 (C_{ipso}), 129.2 (2 C, Ar), 128.6 (2 C, Ar), 127.4 (Ar), 122.2 (2 C, Ar), 119.0 (C_{ipso}), 81.0 (NCH_2O), 55.8 (CH_2Ph), 51.1 ($ArCH_2N$), 35.0, 34.4 ($C(CH_3)_3$), 31.7, 29.8 ($C(CH_3)_3$) ppm. Anal. Calcd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 82.12; H, 10.22; N, 3.84.

(9) Compound **7d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1 H, Ar), 7.75 (s, 1 H, Ar), 7.37 (m, 14 H, Ar), 6.93 (d, J_{HH} = 2.23 Hz, 1 H, Ar), 5.92 (s, 1 H, OCHPhN), 4.98 (s, 1 H, ArCHPhN), 3.94 (d, J_{HH} = 13.95 Hz, 1 H, CH_2Ph), 3.49 (d, J_{HH} = 13.96 Hz, 1 H, CH_2Ph), 1.66 [s, 9 H, $C(CH_3)_3$], 1.37 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C-{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.5, 141.9, 139.5, 138.9, 136.8 (C_{ipso}), 129.2 (2 C, Ar), 129.1 (2 C, Ar), 128.3 (2 C, Ar), 128.2 (2 C, Ar), 128.0 (2 C, Ar), 127.7, 127.0, 126.9 (Ar), 126.6 (2 C, Ar), 125.2, 122.5 (Ar), 118.5 (C_{ipso}), 85.7 (ArCHPhN), 60.8 (NCHPhO), 49.4 (CH_2Ph), 35.1, 34.3 [$C(CH_3)_3$], 31.6, 29.9 [$C(CH_3)_3$] ppm. Anal. Calcd for $C_{35}H_{39}NO$: C, 85.84; H, 8.03; N, 2.86. Found: C, 84.87; H, 8.51; N, 3.56.

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(11) Compound **7e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, J_{HH} = 7.41 Hz, 2 H, Ar), 7.56 (d, J_{HH} = 7.48 Hz, 2 H, Ar), 7.45 (m, 5 H, Ar), 7.73 (m, 2 H, Ar), 7.07 (d, J_{HH} = 2.23 Hz, 1 H, Ar), 5.78 (s, 1 H, NCHPhO), 5.20 (s, 1 H, ArCHPhN), 3.01 (m, 1 H, CH_2), 2.84 (m, 1 H, CH_2), 2.72 (m, 1 H, CH_2), 2.55 (m, 1 H, CH_2), 2.24 [s, 6 H, $N(CH_3)_2$] 1.66 [s, 9 H, $C(CH_3)_3$], 1.44 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C-{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 152.8, 144.6, 138.7, 137.0, 135.4 (C_{ipso}), 129.1 (2 C, Ar), 128.0 (4 C, Ar), 126.5 (2 C, Ar), 125.0, 123.8, 122.5 (Ar), 118.9 (C_{ipso}), 85.7 (NCHPhO), 63.2 (ArCHPhN), 59.1 (CH_2), 45.4 [$N(CH_3)_2$], 43.2 (CH_2), 35.1, 34.8 [$C(CH_3)_3$], 31.6, 29.9 [$C(CH_3)_3$] ppm. Colourless crystals of **7e** suitable for X-ray diffraction were obtained from a MeOH solution at –20 °C. Anal. Calcd for $C_{32}H_{42}N_2O{\cdot}C_{14}H_{22}O$: C, 81.65; H, 9.29; N, 4.23. Found: C, 81.47; H, 10.11; N, 4.17.

(12) Supplementary crystallographic data for **7e** and **10e** may be obtained from the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/data_request/cif or by E-mail to data_request@ccdc.cam.ac.uk) under the deposit numbers CCDC 773865 and CCDC 773866, respectively.

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(14) Compound **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, J_{HH} = 8.3 Hz, 2 H, Ar), 7.50 (d, J_{HH} = 8.1 Hz, 2 H, Ar), 7.22 (d, J_{HH} = 1.9 Hz, 1 H, Ar), 6.69 (d, J_{HH} = 1.8 Hz, 1 H, Ar), 4.94 (s, 1 H, ArCHPhN), 2.75 (m, 2 H, CH_2), 2.59 (m, 2 H, CH_2), 2.42 (m, 1 H, CH_2), 2.21 [s, 6 H, $N(CH_3)_2$] 1.44 [s, 9 H, $C(CH_3)_3$], 1.21 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C-{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 154.4, 146.3, 140.7, 136.7 (C_{ipso}), 129.6 (Ar), 128,1 (2 C, Ar), 125.9 (2 C, Ar), 123.7, 123.4 (Ar), 68.3 (ArCHPhN), 58.4 (CH_2), 45.5 [$N(CH_3)_2$], 45.2 (CH_2), 35.2, 34.3 [$C(CH_3)_3$], 31.8, 29.8 [$C(CH_3)_3$] ppm. In this case, small amounts of the corresponding benzoxazine were also detected.

Compound **8b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, J_{HH} = 8.4 Hz, 2 H, Ar), 7.26 (d, J_{HH} = 8.4 Hz, 2 H, Ar), 7.21 (d, J_{HH} = 2.3 Hz, 1 H, Ar), 6.66 (d, J_{HH} = 2.2 Hz, 1 H, Ar), 4.86 (s, 1 H, ArCHPhN), 2.72 (m, 2 H, CH_2), 2.58 (m, 1 H, CH_2), 2.36 (m, 1 H, CH_2), 2.19 [s, 6 H, $N(CH_3)_2$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.21 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C-{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 154.4, 141.3, 140.5, 136.5 (C_{ipso}), 132.0 (2 C, Ar), 129,6 (2 C, Ar), 123.8 (C_{ipso}), 132.0, 129.5 (Ar), 121.6 (C_{ipso}), 67.9 (ArCHPhN), 58.4 (CH_2), 45.5 [$N(CH_3)_2$], 45.1 (CH_2), 35.2, 34.3 [$C(CH_3)_3$], 31.8, 29.8 [$C(CH_3)_3$] ppm.

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(16) Compound **10a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (m, 2 H, Ar), 7.37 (m, 3 H, Ar), 7.31 (d, J_{HH} = 2.20 Hz, 1 H, Ar), 6.96 (d, J_{HH} = 2.15 Hz, 1 H, Ar), 3.92 (s, 2 H, $ArCH_2N$), 3.86 (s, 2 H, CH_2Ph), 1.38 [s, 9 H, $C(CH_3)_3$], 1.23 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C-{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 151.3, 144.4, 141.4 (C_{ipso}), 130.1 (2 C, Ar), 130.0 (C_{ipso}), 129.4 (Ar), 129.1 (2 C, Ar), 126.9, 125.7 (Ar), 121.3 (C_{ipso}), 49.4 ($ArCH_2N$), 46.5 (CH_2Ph), 35.1, 34.3 [$C(CH_3)_3$], 31.4, 30.1 [$C(CH_3)_3$] ppm. Anal. Calcd for $C_{22}H_{31}NO{\cdot}2.12$ (CH_3OH): C, 73.37; H, 10.13; N, 3.53. Found: C, 73.33; H, 9.80; N, 3.66.

Compound **10b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (s, 1 H, Ar), 7.07 (s, 1 H, Ar), 3.97 (s, 2 H, $ArCH_2N$), 2.69 (m, 1 H, CH, Cy), 1.97 (m, 2 H, CH_2, Cy), 1.73 (m, 2 H, CH_2, Cy), 1.62 (m, 1 H, CH_2, Cy), 1.42 [s, 9 H, $C(CH_3)_3$], 1.29 [s, 9 H, $C(CH_3)_3$], 1.19 (m, 5 H, CH_2, Cy) ppm. ^{13}C-{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 152.7, 142.8, 129.0 (C_{ipso}), 125.9, 124,3 (Ar), 121.6 (C_{ipso}), 56.9 (CH, Cy), 47.1 ($ArCH_2N$), 35.2, 34.4 [$C(CH_3)_3$], 31.5, 30.1 [$C(CH_3)_3$], 29.8 (2 C, CH_2, Cy), 25.3 (CH_2, Cy), 24.9 (2 C, CH_2, Cy) ppm. Anal. Calcd for $C_{21}H_{35}NO{\cdot}2.64$ (CH_3OH): C, 70.62; H, 11.42; N, 3.48. Found: C, 70.54; H, 10.50; N, 3.96.