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Effective synthesis of *ortho*-substituted triphenol amines via reductive amination

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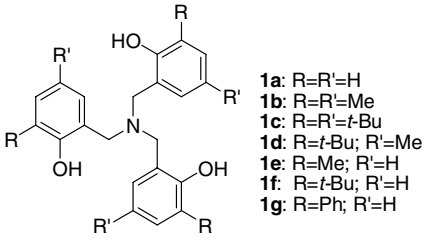
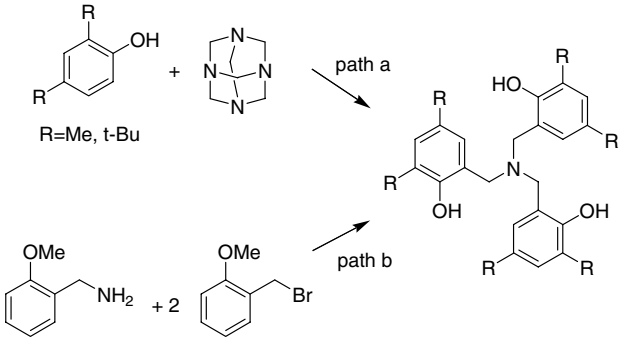
Abstract—An efficient synthesis of *ortho*-substituted triphenolamines via reductive amination is reported. This approach allows access to this increasingly important class of ligands in a structurally systematic way using either commercially or easily synthesizable building blocks.

Recently, a substantial number of publications has appeared regarding the complexation behavior of triphenolamines **1a–d** with a wide variety of transition metals (Ti(IV),[1–9] Zr(IV),[10] In(III),[11] Ga(III),[11] Fe(III),[12] Ta(V),[3,13–15] Al(III)[9,16]) and main group elements (Si(IV)[17–19] and P(V)[20]), together with some reports that deal with the catalytic behavior of some of these complexes, particularly in polymerization reactions.[1,3–6,10,15] In these ligands, especially the substituents in the phenolic *ortho*-position are important as these are in close vicinity to the coordination sphere of the metal center and can therefore be used as control element.[2,7]



1a: R=R'=H
1b: R=R'=Me
1c: R=R'=*t*-Bu
1d: R=*t*-Bu; R'=Me
1e: R=Me; R'=H
1f: R=*t*-Bu; R'=H
1g: R=Ph; R'=H

The synthesis of triphenolamines **1** is usually performed either via a one step Mannich reaction of disubstituted phenols with hexamethylenetetraamine[18] (Scheme 1, path a) or via alkylation of 2-methoxybenzylamine with 2 equiv. of 2-methoxybenzylbromide[12] (Scheme 1, path b). The first synthesis can be applied only to *p*-substituted phenols and affords the products in 40–70% yields after rather long reaction times (2 weeks), while the second requires two different phenolic reagents and protection of the OH functions as methylethers. It has been applied to the synthesis of the unsubstituted compound **1a** ($R = R' = H$) affording the product, after removal of the protecting groups with $AlCl_3$, in 56% overall yield.



Scheme 1. Reported syntheses for triphenolamines **1a–d**. (a) Mannich reaction with 2,4-dialkylphenol and hexamethylenetetraamine, 100 °C, 2 weeks, 40–70%. (b) Double alkylation of 2-methoxybenzylamine and subsequent removal of the methyl groups using $AlCl_3$, 56% overall yield.

Here we report that a series of *ortho*-substituted triphenolamines can be easily and effectively prepared via a different approach: reductive amination of the corresponding salicylic aldehydes. This synthetic approach allows an easy access to a variety of highly pure *ortho*-substituted derivatives under simple and mild reaction

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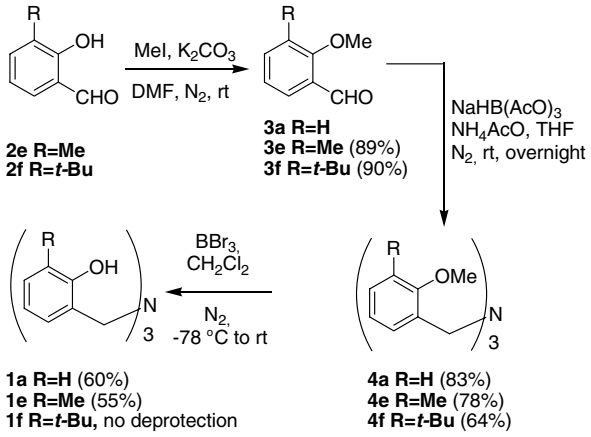
conditions, in short reaction times, satisfactory chemical yields and with easy and efficient purifications. The two key issues that make this method successful and of general application are: (1) the use of $NaBH(AcO)_3/NH_4$-AcO for the reductive amination,[21,22] which allows an effective construction of the ligand skeleton, and (2) the use of a benzyl moiety as protecting group for the phenolic OH, which allows an easy and efficacious purification of the intermediates via chromatography or crystallization and a quantitative removal even in the presence of bulky *ortho* substituents (R = *t*-Bu).[23]

The general strategy that we set up for the synthesis consists in the protection of the OH function of 3-substituted salicyl aldehydes, followed by a threefold reductive amination under conditions similar as reported recently in the literature (NH_4AcO, $NaBH(AcO)_3$, THF).[21] Removal of the protective groups gives triphenol amines **1**. Starting 3-substituted salicyl aldehydes **3** are either commercially available or easily accessible from the corresponding phenol using paraformaldehyde and $MgCl_2$[24] or BuLi and subsequent quenching with DMF.[25]

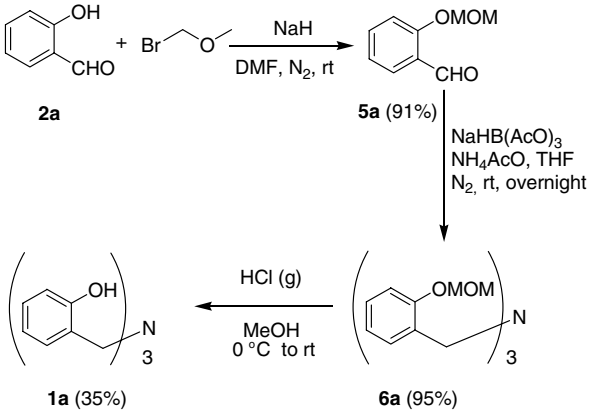
Treatment of commercially available *ortho*-substituted salicyl aldehydes **2e**,**f** with methyliodide in DMF in the presence of potassium carbonate resulted in protection of the phenolic OH in excellent yields (Scheme 2).[26] Subsequently, including commercially available 2-methoxybenzaldehyde **3a**, the threefold reductive amination was performed obtaining the *O*-methyl triphenolamines **4a**,**e**,**f** in 65–80% yields after purification via column chromatography (Al_2O_3 neutral, activity I, EtOAc/hexane = 1:1).[27] However, deprotection of the methyl groups was only partially successful: reaction with boron tribromide in dichloromethane afforded crude triphenolamines **1a** (R = H) and **1e** (R = Me) in 60% and 55% yields, respectively, as confirmed by ^1H NMR spectroscopy and ESI-MS. On the contrary, deprotection of compound **4f**, substituted with *tert*-butylgroups, was not achieved at all, neither using $AlCl_3$ in refluxing toluene. The absence of reactivity may originate from the increased size of the R substituent, which prevents coordination of boron or aluminum to the ethereal functions. Furthermore, although the ^1H NMR spectra of the crude ligands **1a** and **1e** indicated a relatively high purity, these were obtained as brown solids. Repetitive crystallizations from dichloromethane/hexane, with a concomitant significant drop in yield, were necessary to obtain pure white solids.

Alternatively, the use of the MOM protecting group was attempted. Alkylation of salicylaldehyde **2a**[28] and subsequent reductive amination afforded the crude MOM-protected tri-phenol amine **6a** in high yields (87% two steps) (Scheme 3).

However, attempts to purify **6a** via column chromatography using similar conditions as for **4a** (Al_2O_3 neutral, EtOAc/hexane = 1:1) resulted in a very low recovery, typically around 30%. Deprotection of **6a** to give **1a** was attempted using treatment with HCl(g) in MeOH or 6 N HCl in THF (10 min reflux).[25,29,30] The maximum yield obtained was 35% using the first procedure. This rather low yield combined with the difficulties in purifying **6a** made us avoid the use of a MOM-ether as protective group.



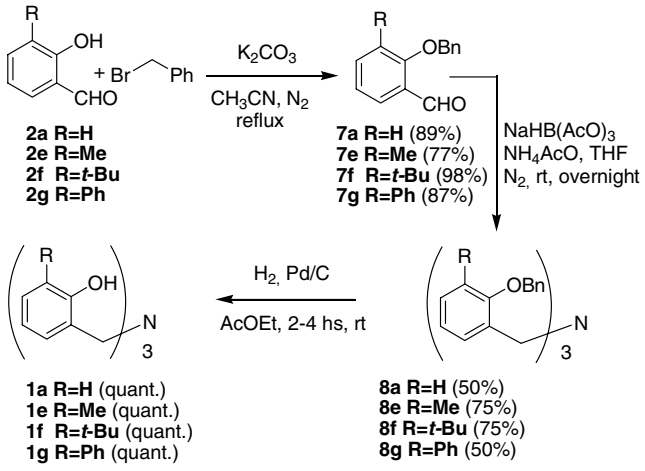
Scheme 2. Synthesis of triphenol amines **1a**,**e**,**f** via reductive amination using an *O*-Me protecting group.



Scheme 3. Synthesis of triphenol amine **1a** via reductive amination using an *O*-MOM protecting group.

Finally, the use of a benzylether as protective group was investigated (Scheme 4). Commonly, this group is conveniently and quantitatively cleaved using H_2 on Pd/C.[31]

3-Substituted salicylic aldehydes **2a**,**e**–**g** were benzylated in 80–90% yield using benzylbromide in acetonitrile in the presence of K_2CO_3.[32] Subsequent reductive amination yielded the desired *O*-benzyl triphenolamines **8** in yields ranging from 50% to 75% after purification. Purification was possible both by recrystallization from either dichloromethane/diethylether or ethanol or column chromatography. Treatment of **8** with 10% Pd/C under an H_2-atmosphere (1 atm) in EtOAc for 3.5 h resulted in a quantitative and clean deprotection. Although for the protecting group removal from derivative **8** the inherent danger exists that cleavage of the tertiary benzylic amine also occurs, no sign of disruption of C–N bonds was observed.[33] Cleavage of these bonds was only observed after a prolonged treatment (15 h)



Scheme 4. Synthesis of triphenol amines **1a**,**e**–**g** via reductive amination using an *O*-benzyl protecting group.

under the reductive conditions, indicating the lower reactivity of the benzylic amine versus the benzylic ether. Triphenolamines **1a**,**e**–**g** were quantitatively obtained as pure white solids, which did not require further purification. Optionally, the ligands can be recrystallized from toluene. The overall yields were in the order of 40–70%.

In conclusion, the reported method allows the synthesis of highly pure *ortho*-substituted triphenolamines **1** with very satisfactory yield. This approach allows, for the first time, access to this increasingly important class of ligands in a structurally systematic way using either commercially or easily synthesizable building blocks. Currently, we are employing this methodology for the synthesis of a large library of this class of ligands for application in coordination chemistry and catalysis.

Acknowledgments

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33. A typical procedure for *O*-benzyl groups deprotection is as follows: Compound **8** was dissolved in degassed AcOEt (~0.05 N) and a catalytic amount of 10% Pd/C was added under a N_2-atmosphere. Next, a H_2-atmosphere (1 atm) was applied and the reaction was stirred for 3.5 h at room temperature. The reaction mixture was filtered over Celite and evaporated to dryness, yielding the final product **1**.
Tri-(2-*hydroxybenzyl*)*amine* **1a**. Compound **1a** was obtained as a white solid (98%). Mp = 151.3–151.7 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.62 (s, 3H, OH), 7.3–7.1 (m, 6H, ArH), 6.8–6.7 (m, 6H, ArH), 3.86 (s, 6H, CH_2N). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 156.3 (C), 131.1 (CH), 129.8 (CH), 122.2 (C), 119.8 (CH), 116.7 (CH), 56.7 (CH_2). ESI-MS: *m*/*z* 336.1592 ($M+H^+$), calcd 336.1600.
Tri-(2-*hydroxy*-3-*methylbenzyl*)*amine* **1e**. Compound **1e** was obtained as a white solid (96%). Mp = 153.6–153.9 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.05 (d, 3H, J = 7.4 Hz, ArH), 6.96 (d, 3H, J = 7.4 Hz, ArH), 6.76 (t, 3H, J = 7.4 Hz, ArH), 6.33 (br s, 3H, OH), 3.73 (s, 6H, NCH_2), 2.26 (s, 9H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 153.7 (C), 131.3 (CH), 128.9 (CH), 125.5 (C), 121.4 (C), 120.2 (CH), 56.4 (CH_2), 16.2 (CH_3). ESI-MS: *m*/*z* 378.2038 ($M+H^+$), calcd 378.2069.
Tri-(2-*hydroxy*-3-*tert-butylbenzyl*)*amine* **1f**. Compound **1f** was obtained as a white solid (92%). Mp = 166.4–166.7 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.27 (d, 3H, J = 7.2 Hz, ArH), 7.00 (d, 3H, J = 7.2 Hz, ArH), 6.81 (t, 3H, J = 7.2 Hz, ArH), 6.55 (br s, 3H, OH), 3.66 (s, 6H, NCH_2), 1.41 (s, 27H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 153.9 (C), 137.6 (C), 129.3 (CH), 127.4 (CH), 122.6 (C), 120.0 (CH), 56.4 (CH_2), 34.8 (C), 29.7 ($3 \times CH_3$). ESI-MS: *m*/*z* 504.3504 ($M+H^+$), calcd 504.3478.
Tri-(2-*hydroxy*-3-*phenylbenzyl*)*amine* **1g**. Compound **1g** was obtained as a white solid (95%). Mp = 157.7–158.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.32 (m, 15H, ArH), 7.16 (m, 6H, ArH), 6.88 (m, 3H, ArH), 3.89 (s, 6H, CH_2N). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 152.5 (C), 137.7 (C), 130.4 (CH), 130.0 (CH), 129.5 (CH), 128.9 (CH), 128.8 (C), 127.6 (CH), 123.5 (C), 120.1 (CH), 55.9 (CH_2). ESI-MS: *m*/*z* 564.2552($M+H^+$), calcd 564.2539.