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A high yielding one-pot method for the preparation of salen ligands

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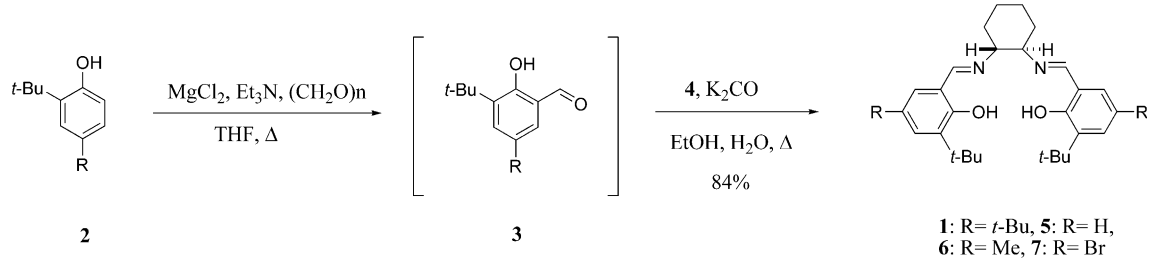
Abstract—Phenols are converted to salicylaldehydes with paraformaldehyde, $MgCl_2$–Et_3N in THF, and subsequently treated with (+)-(*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt affording the corresponding salen ligands in high yields. The reactions are conveniently carried out as a one-pot procedure.

Manganese(III) chloride complexed with the salen ligand (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butyl-salicylidene)-1,2-cyclohexanediamine (**1**), the Jacobsen catalyst, is among the most versatile catalysts for the preparation of homochiral epoxides from alkenes.[1] Salens are also used as ligands for other catalysts of importance in asymmetric synthesis.[1] Jacobsen and Larrow[2] have published a detailed procedure for the preparation of ligand **1**, starting from 2,4-di-*tert*-butylphenol (**2**). In the first step the phenol was transformed into the corresponding 2,5-di-*tert*-butylsalicylaldehyde (**3**), which in a separate step was condensed with (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt (**4**)[3] to give the ligand **1**. The formylation is the critical step of the reaction sequence. The Duff reaction gave a better yield of the salicylaldehyde than either the tin tetrachloride catalyzed formylation or the Reimer–Tiemann reaction;[4] however, the overall yield of the ligand **1** was only in the range of 35–45%, which certainly leaves room for improvement.

We have recently reported a method for the selective *ortho*-formylation of phenols.[5] The method consists of heating under reflux a mixture of a phenol, paraformaldehyde, anhydrous magnesium dichloride, and triethylamine in a solvent. From alkyl- and halogen-substituted phenols, in particular, the corresponding salicylaldehydes were obtained in excellent yields. Applying this simple procedure to the phenol **2** using THF as solvent, the salicylaldehyde **3** was obtained in 85% yield, which is almost twice the yield reported from the Duff reaction.[4] However, it was later proved unnecessary to actually isolate the aldehyde **3**, but rather treat it directly with the salt **4** (Scheme 1).

According to this one-pot procedure, an aqueous ethanol solution of **4** and potassium carbonate was added at ambient temperature to the mixture from the formylation reaction. After 4 h of heating at 80 °C the aldehyde had been consumed. Recrystallization of the



2 **3** **1**: R= *t*-Bu, **5**: R= H, **6**: R= Me, **7**: R= Br

Scheme 1.

Keywords: *ortho*-Formylation of phenols; Jacobsen ligand; Salen ligands.
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residue from acetone afforded the salen ligand **1** in 84% yield, based on the phenol **2**, exhibiting spectral data in accordance with those reported.[4] Experimental details for the preparation of **1** are given below.[6]

The usefulness of this one-pot method is not limited to the preparation of the salen ligand **1**. The ligands **5**, **6**, and **7**[4] were prepared from the corresponding phenols in 85%, 93%, and 80% yields, respectively.

In conclusion, using this simple one-pot procedure, salen ligands are available from the respective phenols in considerably better overall yields than those previously reported.

References and notes

1. Larrow, J. R.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *6*, 123–152.
2. Jacobsen, E. N.; Larrow, J. R. *Org. Synth.* **1998**, *75*, 1–11.
3. Gasbøl, F.; Steenbøl, P.; Sørensen, B. S. *Acta Chem. Scand.* **1972**, *26*, 3605–3611.
4. Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939–1942.
5. Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, *53*, 258–262.

6. Preparation of **1**: to a stirred suspension of 2,4-di-*tert*-butylphenol (**2**) (4.12 g, 20 mmol), anhydrous $MgCl_2$ (3.81 g, 40 mmol) and dry paraformaldehyde (1.32 g, 44 mmol) in dry THF (80 mL), kept at ambient temperature, was added dropwise dry Et_3N (4.05 g, 40 mmol). The green-colored reaction mixture was then heated to gentle reflux for 2 h. GLC analysis showed complete conversion of starting materials to 3,5-di-*tert*-butyl salicylaldehyde. A solution of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (2.65 g, 10 mmol) and K_2CO_3 (3.12 g, 22.5 mmol) in ethanol–water (1:1, 30 mL) was added dropwise at ambient temperature. After addition was complete, the reaction mixture was heated for 4 h at 80 °C. The yellow-colored reaction mixture was cooled and added to water. The product was extracted with CH_2Cl_2 (3×100 mL), the combined organic fractions were washed with water (50 mL), brine (2×50 mL), and dried ($MgSO_4$). Removal of solvents afforded a yellow solid that was recrystallized from acetone (1:20 w/v) to give (−)-(*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butyl)-salicylidene)-1,2-cyclohexanediamine (**1**) as a yellow powder (84% yield), mp 201–204 °C; lit.[4] 200–203 °C; ^{1}H NMR (300 MHz): δ 13.74 (s, 2H), 8.33 (s, 2H), 7.31 (d, $J = 2.1$ Hz, 2H), 7.02 (d, $J = 2.1$ Hz, 2H), 3.70–3.30 (m, 2H), 2.00–1.30 (m, 6H), 1.45 (s, 20H), 1.25 (s, 18H); ^{13}C NMR (75 MHz): 165.9, 158.2, 139.9, 136.4, 126.7, 126.2, 117.9, 72.5, 35.2, 34.1, 33.4, 29.6, 24.4; $[\alpha]_D^{22}$ −312 (*c* 1.0, CH_2Cl_2), lit.[4] $[\alpha]_D^{22}$ −315 (*c* 1.0, CH_2Cl_2).