High-Yielding Large-Scale Syntheses of Enantiomerically Pure NOBIN and a NOBIN-Based Enantiomerically Pure NHC Precursor

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Abstract: The MOM-protected monotriflate derived from enantiomerically pure (*S*)-BINOL rendered (*S*)-NOBIN (67% over 5 steps) and an (*S*)-configured NHC precursor (55% over 5 steps) on 10 gram and 5 gram scales, respectively. The C–N bond formation was realized by OTf → NHBn and OTf → NH–CH_2–CH_2–NH–mesityl exchanges, respectively.

Key words: BINOL, Buchwald–Hartwig amination, imidazolinium chloride, ligand synthesis, N-heterocyclic carbene, NOBIN

Enantiomerically pure NOBIN[1] [e.g., (*S*)-**1** (Figure 1)] is an organocatalyst[2] and precursor of ligands used for asymmetric addition of diethylzinc to aromatic aldehydes,[3] for Ti-catalyzed Mukaiyama aldol additions to aldehydes[4] or hetero-Diels–Alder reactions between aldehydes and Danishefsky's diene,[5] for Cu-catalyzed 1,4-additions of Et_2Zn to enones,[6] for Ru-catalyzed cyclopropanations with diazoacetates[7] or transfer hydrogenations of acetophenones,[8] and for Rh-catalyzed enecyclizations of 1,6-enynes.[9] Expanding the usefulness of (*S*)-NOBIN in asymmetric catalysis, Hoveyda et al. converted it into the *S*-configured NHC precursor **2**[10] and employed the latter in the following transformations: Cu-catalyzed 1,4-addition of organozinc compounds to cycloalkenones,[11] Cu-catalyzed allylation of organozinc compounds with allylic phosphates,[12] and Ru-catalyzed ring-closing metathesis or ring-opening metathesis–cross-metathesis tandem reactions.[10,13] We have modified the published route to (*S*)-**1** and simplified the access to (*S*)-**2** and disclose here how we proceeded.

(*S*)-NOBIN (**1**) results from the asymmetric oxidative coupling of 2-naphthol and 2-naphthylamine with 46% ee[14] at most.[15] The Brunner[8]–Hoveyda[10] synthesis of **1** starts by an ArS_N reaction between 2-methoxynaphth-1-ylmagnesium bromide and (–)-menthyl 1-(–)-menthyloxy-2-naphthoate and a difficult separation of the resulting atropisomers. Obviating such purification problems the Singer–Buchwald synthesis[16] of **1** starts from relatively inexpensive[17] (*S*)-BINOL (**3**) and conserves its stereohomogeneity throughout six refunctionalization steps (Scheme 1).

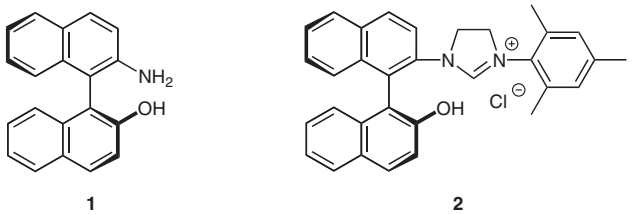
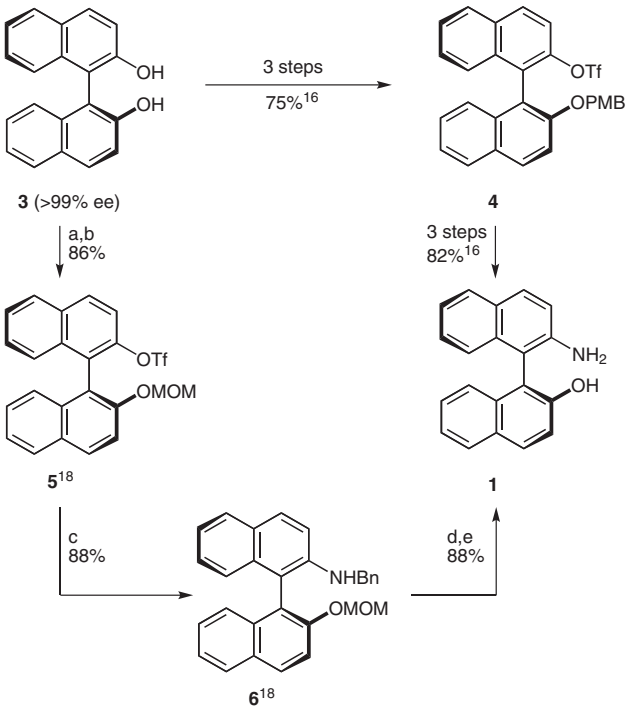


Figure 1 (*S*)-NOBIN (**1**) and the (*S*)-NOBIN-based NHC precursor **2**



Scheme 1 Syntheses of (*S*)-NOBIN (**1**) from (*S*)-BINOL (**3**) according to ref. 16 – via the PMB-protected monotriflate **4** – and by ourselves – via the MOM-protected monotriflate **5**. *Reagents and conditions*: a) Tf_2O (1.0 equiv), *i*-Pr_2NEt (1.0 equiv), CH_2Cl_2, 0 °C, 2 h; 91% (ref. 18: ≥97%); b) P_4O_{10} (1.0 equiv), $CH_2(OMe)_2$, CH_2Cl_2, r.t., 7 h; 95%; c) $BnNH_2$ (1.3 equiv), Cs_2CO_3 (1.3 equiv), $Pd(OAc)_2$ (10 mol%), (*o*-$Ph_2PC_6H_4)_2O$ (20 mol%), toluene, 115 °C, 6 h; 88% (ref. 18: ≥91%); d) H_2 (1 atm), Pd/C (5 mol%), EtOAc, 60 °C, 7 h; e) H_2SO_4, MeOH, CH_2Cl_2, reflux, 4 h; 88% over the 2 steps; MOM = CH_2OMe; PMB = *p*-methoxybenzyl; Tf = SO_2CF_3.

We converted (*S*)-BINOL into **1** via (*S*)-BINOL monotriflate, the derived MOM ether **5**, and the corresponding benzylaminolysis product **6**. This sequence was known[18] except that we[19] methoxymethylated the monotriflate with dimethoxymethane and phosphorus pentoxide[20] and thereby avoided the use of chloromethyl methyl ether.[18] The latter is carcinogenic and classified as an extremely

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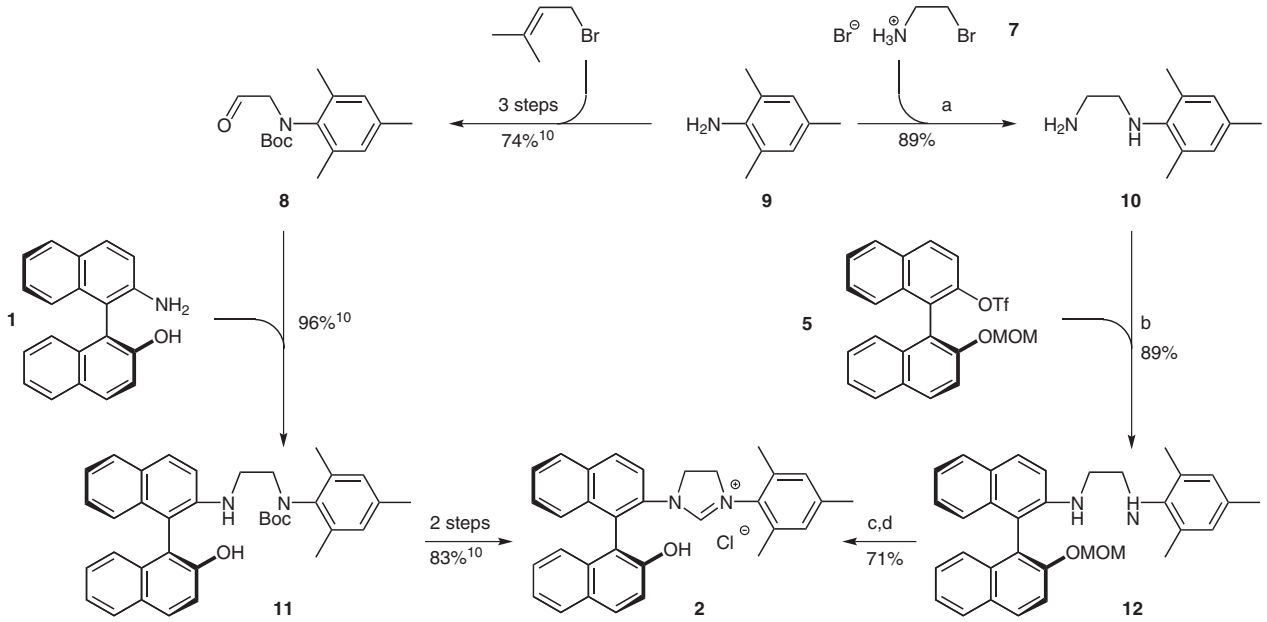

Scheme 2 Syntheses of the (*S*)-configured NHC precursor **2** from (*S*)-NOBIN (**1**) according to ref. 10 or from the MOM-protected monotriflate **5** by ourselves. *Reagents and conditions*: a) **9** (3.0 equiv), toluene, reflux, 23 h; 89% (ref. 24: 86%); b) **10** (1.3 equiv), Cs_2CO_3 (1.3 equiv), $Pd(OAc)_2$ (10 mol%), $(o\text{-}Ph_2PC_6H_4)_2O$ (20 mol%), toluene, 115 °C, 14 h; 89%; c) concd aq HCl–MeOH (1:20), reflux at 0.1 M, 9 h; d) $HC(OEt)_3$, EtOH (discharged during the reaction by a current of N_2), 125 °C, 26 h; 71% over the 2 steps.

hazardous chemical by the EU and the EPA.[21] The yield of benzylamine **6** was 76% overall. Debenzylation of **6** with 1 bar hydrogen and methanolysis of the MOM group furnished 10 g batches of (*S*)-NOBIN (**1**) in 88% yield.[22] All in all our route is slightly better yielding (65%) than Buchwald's (62%) and significantly cheaper: Starting from commercially available reagents, benzophenone imine alone – required for the aminolysis of **4** according to ref. 16 – costs more than our whole synthesis.

To date, the *S*-configured NHC precursor **2** has been synthesized only by the Hoveyda group (Scheme 2, left):[10] Boc protection of mesitylamine (**9**), prenylation, and ozonolysis led to the protected aminoaldehyde **8**. The latter was condensed with (*S*)-NOBIN (**1**) reductively ($NaBH_3OAc$), providing aminocarbamate **11**. Deprotection rendered a bis(amine hydrochloride), which was suspended in triethyl orthoformate and heated until **2** had formed.

Our synthesis of compound **2** starts from the MOM-protected monotriflate **5** (Scheme 2, right), which preceeds (*S*)-NOBIN (**1**) by three steps in the synthetic sequence of Scheme 1 and is therefore more readily accessible (or costs significantly less[17,23]). Buchwald–Hartwig amination of monotriflate **5** with *N*-mesityl ethylenediamine (**10**[24,25]) furnished 89% of the MOM-protected diamine **12**[26] in what appears to be the first example of such a reaction between an aryl triflate and an unprotected *N*-aryl ethylenediamine. The overall yield of diamine **12** from (*S*)-BINOL was 77%. Removal of the MOM group with hydrochloric acid rendered the bis(amine hydrochloride) described by Hoveyda.[10] In our hands cyclocondensation of this compound in triethyl orthoformate under the reported conditions[10] gave no more than 40% yield – presumably because the reaction medium was heterogeneous all the time. In fact we found it difficult to follow the advice[10] to scrape unreacted starting material from the inside wall of the flask since it stuck there as if gluing. We made such measures obsolete by running the same reaction in a homogeneous phase, namely a 1:4 mixture of ethanol and triethyl orthoformate. Under these modified conditions we isolated 71% of the NHC precursor **2**.

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(17) Enantiopure BINOL: 5 g ca. 50 € [(*R*)-BINOL, ABCR; (*S*)-BINOL, AlfaAesar), 1 kg ca. 900 $ [(*R*)- or (*S*)-BINOL, AK Scientific).
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(19) (*S*)-BINOL monotriflate (5.59 g, 13.4 mmol) was dissolved in CH_2Cl_2 (35 mL) and $CH_2(OMe)_2$ (35 mL). Then P_4O_{10} (3.93 g, 13.8 mmol, 1.03 equiv) was added within 1 h in 2 portions. The mixture was stirred at r.t. for 7 h, poured into aq NH_3 (35%, 30 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and flash chromatography on SiO_2 (eluent: cyclohexane–EtOAc, 95:5) provided the MOM-protected (*S*)-BINOL monotriflate **5**[18] (5.90 g, 95%) as a colorless oil. It crystallized slowly when transferred into a refrigerator.
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(22) A suspension of benzylamine **6** (15.9 g, 38.0 mmol) and Pd (10% on C, 2.04 g, 1.99 mmol, 5 mol%) in EtOAc (70 mL) was heated under H_2 (1 atm) at 60 °C for 3 h. After filtration through Celite, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and MeOH (100 mL). Concentrated H_2SO_4 (6.0 mL) was added and the mixture refluxed for 2 h. Saturated aq $NaHCO_3$ (100 mL) was added after cooling. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure provided (*S*)-NOBIN (**1**; 9.19 g, 85%) as a faintly yellow solid (pure as judged by ^{1}H NMR). Recrystallization from toluene rendered rounded white needles (8.84 g, 82%). On a smaller scale (3.29 g of benzylamine **6**) the yield of recrystallized **1** was 1.97 g [88%; cf. footnote (e) of Scheme 1].
(23) Enantiopure NOBIN: 1 g ca. 500 € [(*R*)- or (*S*)-NOBIN, ABCR], 10 g ca. 1500 $ [(*R*)-NOBIN], 50 g ca. 4000 $ [(*S*)-NOBIN, both Shanghai FWD Chemicals].
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(25) Simplified Synthesis of Diamine 10[24]
A suspension of 2-bromoethylamine hydrobromide (**7**; 8.24 g, 40.2 mmol) and mesitylamine (**9**; 16.0 g, 119 mmol, 2.94 equiv) in toluene (160 mL) was refluxed for 23 h. After cooling, aq NaOH (20%, 120 mL) was added. The mixture was extracted with EtOAc (3 × 120 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and flash chromatography on SiO_2 (eluent: EtOAc, then EtOAc–MeOH, 1:1 + 1% Et_3N) provided **10** (6.39 g, 89%) as a deep red oil.
(26) The following conditions were adapted from a related transformation:[18] Cs_2CO_3 (7.51 g, 23.0 mmol, 1.30 equiv) was dried in vacuo with a heat gun for 30 min. After cooling, $Pd(OAc)_2$ (395 mg, 1.76 mmol, 9.90 mol%), (o-$Ph_2PC_6H_4)_2O$ (1.89 g, 3.51 mmol, 20 mol%), and a solution of the MOM-protected monotriflate **5** (8.22 g, 17.8 mmol) and the diamine **10** (4.09 g, 22.9 mmol, 1.29 equiv) in toluene (9 mL) were added. The suspension was degassed and stirred at 115 °C for 14 h. Filtration through Celite, evaporation of the solvent under reduced pressure, and flash chromatography on SiO_2 (eluent: cyclohexane–EtOAc, 90:10 → 80:20) provided the diamine **12** (7.79 g, 89%) as a reddish-brown sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.91 (s, 2 × o-CH_3), 2.17 (s, p-CH_3), 2.95 (ddd, ^3J = ^3J = 5.5 Hz, ^3J = 2.2 Hz, NCH_2), 3.12 (s, OCH_3), AB signal (δ_A = 3.33 ppm, δ_B = 3.39 ppm, J_{AB} = 13.0 Hz, in addition split by J_A = J_B = 5.7 Hz, NCH_2), 3.85 (br s, 2 × NH), AB signal (δ_A = 4.97 ppm, δ_B = 5.02 ppm, J_{AB} = 6.8 Hz, OCH_2O), 6.71 (s, 2 × mesityl-H), 6.94–6.97 (m, ArH), 7.11–7.19 (m_c, 2 × ArH), 7.21–7.23 (m, 2 × ArH), 7.24–7.27 (m, ArH), 7.35 (ddd, ^3J = 8.1 Hz, ^3J = 5.8 Hz, ^3J = 2.3 Hz, ArH), 7.55 (d, ^3J = 9.1 Hz, ArH), 7.76–7.78 (m, ArH), 7.86 (d, ^3J = 8.1 Hz, ArH), 7.87 (d, ^3J = 8.9 Hz, ArH), 7.95 (d, ^3J = 9.0 Hz, ArH). HRMS (EI, 70 eV): *m/z* calcd for $C_{33}H_{34}N_2O_2$ [M$^+$]: 490.262028; found: 490.262202 (+0.4 ppm). $[\alpha]_D^{20}$ –75 (*c* 1.05, $CHCl_3$).