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Efficient synthesis of 6-mono-bromo-1,1′-bi-2-naphthol

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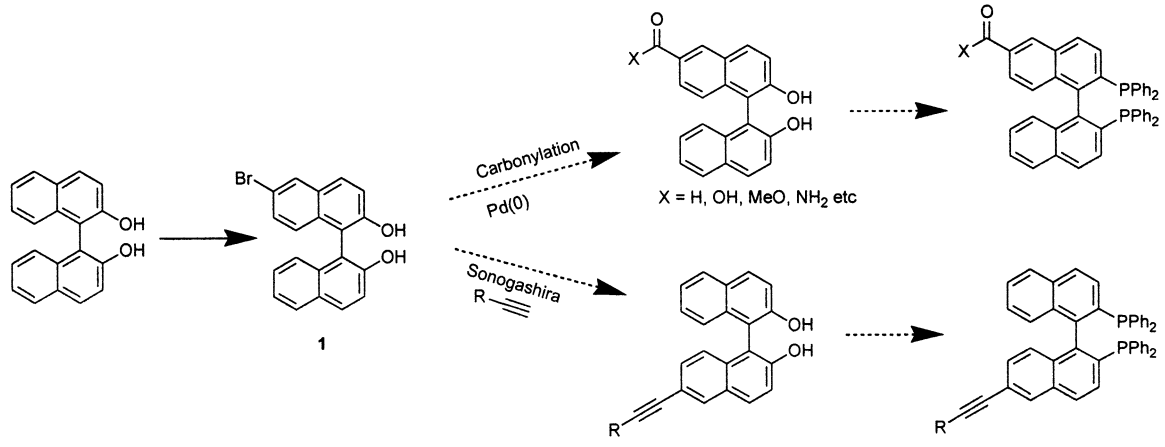
Abstract—Through mono-ester formation of 1,1′-bi-2-naphthol (BINOL) with pivaloyl chloride the selective mono-bromination was achieved cleanly on the other ring to afford 6-mono-bromo-1,1′-bi-2-naphthol in an efficient 86% yield.

Polymer supported reagents and catalysts are very valuable and offer many advantages such as easy isolation, recovery and re-use.[1] Notwithstanding, there are also disadvantages due mainly to the extra cost associated with the catalyst preparation of properly functionalized chiral ligands. By using suitable solid supports, polymer-supported catalysts can achieve similar selectivity and reaction rates as traditional homogeneous catalysts.[2] Most chiral ligands are C2 symmetric,[3] which makes them difficult to functionalize selectively for attachment to the polymer support. We chose to study the binaphthyl system as a useful chiral scaffold through the preparation of mono-bromo-1,1′-bi-2-naphthol (**1**). From this molecule, a variety of functionalized derivatives of BINOL and BINAP (bisdiphenylphosphino-1,1′-binaphthyl) could be prepared for polymer supports (Scheme 1).[4,5] Although one can prepare 6-monobromo-1,1′-bi-2-naphthol easily via non-selective methods, such as oxidative coupling between 6-bromo-naphth-2-ol and naphth-2-ol, controlled bromination of 1,1′-bi-2-naphthol, or debromination of 6,6′-dibromo-1,1′-bi-2-naphthol,[1c,6] further purification by chromatography is generally required. Here we wish to report a very efficient synthesis of 6-mono-bromo-BINOL from BINOL in 86% isolated yield without the need for column purification.

Our strategy was to first prepare the monoester of 1,1′-bi-2-naphthol selectively (Scheme 2). Since the two hydroxy groups are in close proximity to each other, mono-functionalization may be possible using a bulky acylating agent. After several reagents were explored, 1 equiv. of pivaloyl chloride provided excellent selectivity at 95:4:1 (product: bis-ester: starting material). Simple



Scheme 1. Transition metal-catalyzed cross coupling reactions.

Keywords: 6-mono-bromo-1,1′-bi-2-naphthol; bromination.

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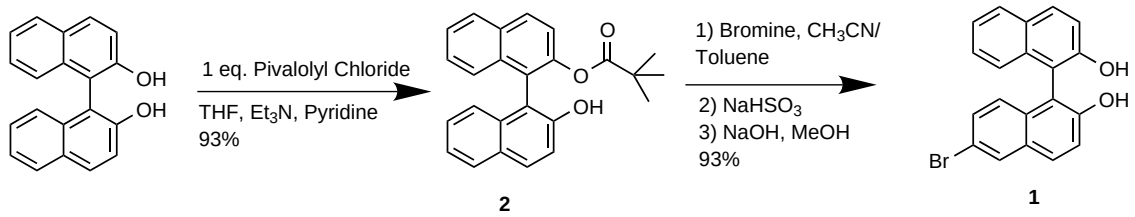

Scheme 2.

aqueous workup and crystallization from hexane (10 mL/g) afforded pure mono-pivaloate **2** (99.6% purity) in 93% isolated yield.[7] With one of the naphthol rings deactivated, mono-bromination was selective at the 6-position of the other naphthol. After bromination, in situ saponification and simple aqueous work up, crystallization from hexane/MTBE (3:1) afforded pure 6-mono-bromo-1,1-bi-2-naphthol (**1**) in 93% isolated yield with 98.9% purity. Chiral resolution using our previously published procedure worked very well and either enantiomer could be obtained with >98% ee.[8,9]

In conclusion, we have demonstrated a practical method to produce either enantiomer of 6-mono-bromo-1,1′-bi-2-naphthol (**1**) in 86% overall yield. Selective ester formation can be carried out with pivaloyl chloride. Through deactivation of one naphthyl ring the other ring can in turn undergo selective bromination. The bromide is expected to offer an effective handle for attachment to a solid support for use as a supported ligand in catalysis.

Experimental

To a solution of 1,1′-bi-2-naphthol (17.2 g, 60 mmol) in THF (150 mL) at 0 to −10°C (ice/acetone) was added triethylamine (12 mL, 86 mmol), pyridine (1.2 mL, 1.5 mmol), followed by pivaloyl chloride (8.1 mL, 66 mmol). The resulting solution was allowed to warm from 0°C to room temperature and aged at room temperature for several hours until the starting material was almost consumed (monitored by HPLC, <1% as judged by HPLC).[10] The reaction mixture was quenched with 150 mL water, pH adjusted to 1 with 6N HCl and extracted with toluene (150 mL). The toluene layer was washed with 0.1N HCl (150 mL), followed by a water wash (150 mL). The organic layer was separated, concentrated under reduced pressure, and the product **2** was crystallized from hexane to afford **2** as a white solid (21.2 g, 95 wt%, 93%) with 2.7% loss in the mother liquid. The isolated product **2** was 99.6% pure with 0.15% starting material and 0.2% bis-pivalate of BINOL. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.08 (d, $J=9$ Hz, 1H); 7.98 (d, $J=8$ Hz, 1H); 7.9 (d, $J=9$ Hz, 1H); 7.84 (dd, $J=1$, 8 Hz, 1H); 7.52 (m, 1H); 7.3 (m, 6H); 7.07 (d, $J=9$ Hz, 1H); 0.8 (s, 9H). ^{13}C NMR ($CDCl_3$, 63 MHz) 177.9; 151.8; 148.3; 133.7; 133.5; 132.2; 130.8; 130.3; 129.0; 128.4; 127.9; 127.5; 126.7; 126.2; 125.7; 124.6; 123.6; 123.1; 121.9; 118.3; 114.3; 38.9; 26.5. Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99. Found: C, 81.07; H, 6.00%.

To a solution of the mono-ester of BINOL **2** (3.60 g, 10 mmol) in 25 mL acetonitrile and 25 mL toluene at 0°C was added bromine (0.55 mL, 10.7 mmol). The reaction mixture was warmed to room temperature and monitored by HPLC. The reaction conversion was only 50% so additional bromine was added (0.45 mL, 8.8 mmol) and the solution was aged for 30 min. The reaction conversion increased to 99% (as judged by HPLC). The reaction was quenched with $NaHSO_3$ (2 g, ~19 mmol, to reduce excess bromine) and NaOH (20 mL, 5N). The saponification was complete in 1 h. The reaction solution was acidified with HCl to pH ~1, then extracted with ethyl acetate (100 mL). The organic layer was separated, washed once with water (100 mL) and concentrated under reduced pressure to an oil. The product **1** was crystallized in 3:1 ratio of hexane:MTBE (30 mL hexane:10 mL MTBE) to afford an off-white solid (3.40 g, 98.9% purity, 93% yield). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.0 (d, $J=8.1$ Hz, 1H); 7.08 (dd, $J=8.1$, 1 Hz, 1H); 7.32 (m, 5H); 7.80 (d, $J=8.8$ Hz, 1H); 7.86 (dd, $J=8.1$, 1 Hz, 1H); 7.91 (d, $J=8.8$ Hz, 1H); 8.0 (d, $J=2.0$ Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 110.2; 111.3; 117.7; 117.8; 118.8; 123.9; 124.1; 126.0; 127.6; 128.4; 129.4; 130.2; 130.3; 130.5; 130.6; 131.5; 132.0; 133.2; 152.6; 152.9. Anal. Calcd for $C_{20}H_{13}BrO_2$: C, 65.77; H, 3.59; Br, 21.88. Found: C, 65.58; H, 3.75; Br, 21.71%.

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7. Purity is reported as HPLC area% at 220 nm. Conditions for HPLC assay were follows: Waters SymmetryShield RP_{18} column, 5 μm, 4.6×250 mm, 20°C, 1.5 mL/min, linear gradient from 60% acetonitrile/water to 90% acetonitrile over 20 min, then hold for 5 min; water contained 0.1% $HClO_4$; UV detection at 220 nm. Typical retention times are 5.1 min (BINOL), 10.0 min (monopivolate **2**), 17.2 min (bis-pivolate), 7.5 min (monobromo BINOL **1**).
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9. Chiral assay of 6-bromo-binol could be achieved using Diacel OD-H column (4.6×250 mm, 5 μm) using 0.05% acetic acid/15% isopropanol/hexane. With 0.8 mL/min flow rate, retention times of two enantiomers are 12.2 and 17.5 min, respectively.
10. Since starting material is more polar and less soluble in hexane. It is not effective to remove starting material by crystallization. It is better to push the reaction to almost completely consumed starting material BINOL (<1% by HPLC).