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Gram Scale Conversion of *R*-BINAM to *R*-NOBIN

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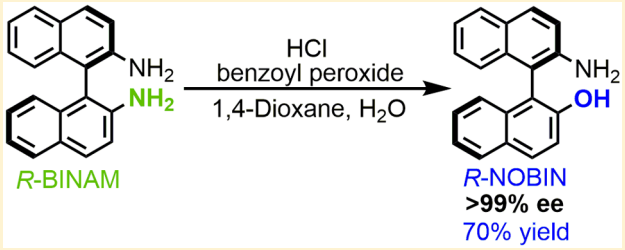
Supporting Information

ABSTRACT: A mild, operationally simple, and single-step transition-metal-free protocol for the synthesis of enantiomerically pure (*R*)-(+)-2′-amino-1,1′-binaphthalen-2-ol (*R*-NOBIN) from (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine (*R*-BINAM) is reported. The one-pot conversion proceeds with good yield and shows no racemization. The hydroxyl on the *R*-NOBIN product was shown to have come from water in the reaction medium via an $H_2{}^{18}O$ study. The correct value of the specific rotation of *R*-NOBIN was reported.



Atropisomers (axially chiral biaryls) are stereoisomers that arise from hindered rotation of two aromatic groups connected by a single C−C bond. This barrier to rotation allows for the isolation of many atropisomers in their single enantiomer forms.[1,2] The biaryl scaffold is considered a privileged structural motif (capable of binding to multiple receptors with high affinity) in pharmaceutical research with demonstrated activity as antitumor, antiamebic, antifungal, antihypertensive, anti-inflammatory, and antirheumatic agents among other therapeutic classes.[3,4] Biaryl backbones, embedded in 4.3% of all known drugs, are of a great significance due to their utility in biomolecular targeting and recognition.[5−8] Substituted biaryls have found a myriad of uses in organic synthesis, natural products chemistry, and material science devices such as light-emitting diodes, solar cells, and photoconductors.[9−11] Atropisomers such as (*R*)-(+)-2′-amino-1,1′-binaphthalen-2-ol (*R*-NOBIN, **3**) have demonstrated usefulness as ligands and chiral auxiliaries in asymmetric catalysis leading to a wide array of catalytic enantioselective conversions.[1,4,9,12−18] Kagan et al. have shown NOBIN's usefulness as a phase transfer catalyst.[19−21] Chiral ligands made from optically pure NOBIN by Carreira have been utilized in numerous Ti-catalyzed aldol reactions.[22−25] NOBIN-derivatized ligands and catalysts have been reportedly used for Michael addition,[26] diethyl zinc addition to aldehydes, allylation of aldehydes, allylic substitutions, 1,4-addition to α,β-unsaturated ketones, intermolecular cyclopropanation,[27] asymmetric metathesis,[28] aldol-type reactions, Diels−Alder and hetero-Diels−Alder reactions, transfer hydrogenation of ketones, α-vinylation of ketones, and Suzuki coupling reactions.[9] Substituting the binaphthyl backbone with a variety of functional groups can alter the electronic and steric properties of the molecule that influence its catalytic behavior.[29] Such modifications of a catalyst can help fine-tune asymmetric synthesis and steer reactions in favor of an enantiomer of interest.[29] Given the varied utility of the atropisomer NOBIN, many attempts were made to synthesize it.

NOBIN was first synthesized as a racemic mixture by Kočovský et al. in 1991, using a Cu(II)Cl_2-mediated oxidative cross-coupling between 2-naphthol and 2-naphthylamine.[30,31] The product mixture also included small amounts of 1,1′-binaphthyl-2,2′-diamine (BINAM) and 1,1′-bi(2-naphthol) (BINOL).[31] An improvement of the aforementioned method was reported by Ding et al. using a two-component molecular crystal and Fe^{3+} as the oxidant in a two-phase reaction.[9,32] Zhang et al. attempted a 20 g synthesis using the above-mentioned two methods and found 40% and 58% yields for racemic NOBIN from Kočovský's and Ding's method, respectively.[33] Zhang cited difficulties in removal of BINAM and BINOL in the product mixture leading to lower yields of NOBIN. With a slight modification to the Kočovský method, Carreira et al. obtained racemic NOBIN in 65% yield (however, in 48 h and with 10 equiv of 2-naphthylamine).[4] Zhang et al. also reported a strategy to obtain racemic NOBIN in 91% yield from BINOL under very harsh reaction conditions (200 °C, 5 days in autoclave).[33] When the same reaction was done with enantiomerically pure BINOL, only the racemic product was formed. Historically, NOBIN syntheses involving conversion from BINOL as well as coupling of 2-naphthol and 2-naphthylamine generally produced BINAM as a byproduct preventing isolation of NOBIN in higher yields.[33,34] Shortly after their original work, Kočovský et al. also attempted enantio-enrichment of binaphthyls in the presence of chiral amines producing *R*-NOBIN in 42% yield with a low 46% ee.[35] The utility of asymmetric synthesis of NOBIN from enantiomerically pure BINOL, such as the one reported by Buchwald et al., is also limited due to several required protection and deprotection steps.[36] In retrospect, attempts at synthesizing NOBIN have faced challenges of low yields, formation of biaryl impurities, and complex reaction procedures (e.g., long reaction times, heavy metal catalysts).[9,14,33,34,37,38]

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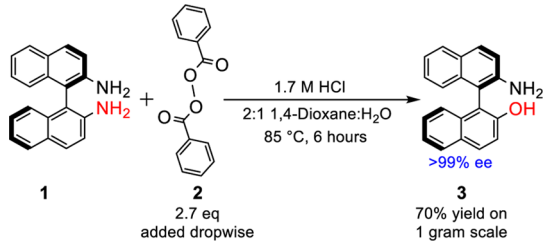
The synthetic problems have resulted in the relatively high cost of enantiomerically pure NOBIN (*R*-NOBIN: $928/g, Sigma-Aldrich) and have constrained it from reaching its full utilitarian potential despite its vast number of possible applications.[9] In this work, a novel one-step and operationally simple conversion of *R*-BINAM (**1**) ($140/g, Sigma-Aldrich) to *R*-NOBIN (**3**) has been reported and optimized for the gram scale. The resulting *R*-NOBIN is enantiomerically pure and eliminates the need to isolate it from a racemate via preparative scale chiral purification, a difficult and expensive procedure. Conversely, the starting material (*R*-BINAM) is relatively straightforward to obtain in high yield and enantiomeric purity.[15,39]

During a study of the racemization rates of **1**, we found that **3** was produced when **1**, dissolved in a mixture of 1,4-dioxane and DI (deionized) water, was heated in the presence of an acid. Upon further examination, it was found that a free radical initiator also was necessary to facilitate the reaction. Benzoyl peroxide (**2**), a diacyl peroxide and an efficient radical initiator, was employed for the task (Scheme 1).[40] The conversion was a

Scheme 1. Synthesis of *R*-NOBIN from *R*-BINAM



one-pot process, and the stereochemistry was maintained throughout the reaction with no traces of *S*-NOBIN observed by chiral high performance liquid chromatography (HPLC). The conversion was also found to be successful in converting *S*-BINAM to *S*-NOBIN in a similar fashion with no racemization. Optimization studies were performed on small scale (1−5 mg), and % conversions reported in Tables 1−4 are from HPLC analysis with 2 h reaction times, unless otherwise stated. Unidentified side products, decomposition products, and impurities will be referred to as impurities henceforth.[41−44]

Table 1. Optimization of Reaction Solvent[a]

entry	organic solvent	organic/aqueous	% conversion of **1** to **3**
1	acetone	2:1	0
2	DMF	2:1	5
3	DMSO	2:1	4
4	IPA	2:1	1
5	THF	2:1	3
6	ACN	2:1	reagents insoluble
7	1,4-dioxane	1:1	reagents insoluble
8	1,4-dioxane	3:2	reagents insoluble
9	1,4-dioxane	2:1	77
10	1,4-dioxane	3:1	65
11	1,4-dioxane	4:1	60
12	1,4-dioxane	5:1	59

[a]Reaction conditions: **1** (5 mg, 17 mM), **2** (1 mol equivalent), various water-soluble organic solvents, and 3.25 M HCl overall heated at 85 °C for 2 h.

Various compositions of water-soluble organic solvents were examined, and their effect on conversion was monitored over the 2 h reaction time (Table 1). 1,4-Dioxane far exceeded other organic solvents in producing a substantial amount of **3** (59−77% conversion, entries 1−6, 9). Surprisingly, the use of THF (entry 5) led to poor product formation (3%) despite being structurally similar to 1,4-dioxane. Use of DMF, DMSO, and IPA (entries 2−4) all showed drastically lower conversion to **3** compared to 1,4-dioxane. Using acetone did not show any formation of the desired product (entry 1). The reagents were insoluble in the acetonitrile/water mixture (entry 6). Various ratios of 1,4-dioxane/water were also monitored (entries 7−12). Ratios with 1,4-dioxane lower than 2 volume equivalents to water led to partially insoluble reagents (entries 7−8). 1,4-Dioxane in 2 volume equivalents to water provided 77% conversion to **3** (entry 9) while higher amounts led to a decrease in production of **3**. Reaction mixtures prepared solely in organic or aqueous solvents were unable to dissolve **1** and/or **2**.

Different radical initiators also affect the reaction (Table 2). Use of 2 mol equiv of azobis(isobutyronitrile) (AIBN), a strong

Table 2. Optimization of Radical Initiator[a]

entry	initiator	**1**/initiator	% conversion of **1** to **3**
1	AIBN	1:2	50
2	$K_2S_2O_8$	1:2	17
3	2-butanone peroxide	1:2	8
4	cumene hydroperoxide	1:2	5
5	*tert*-butyl hydroperoxide	1:2	37
6	H_2O_2	1:2	3
7	lauroyal peroxide	1:2	reagents insoluble
8	benzoyl peroxide	1:0.1	10
9	benzoyl peroxide	1:0.5	21
10	benzoyl peroxide	1:1	75
11	benzoyl peroxide	1:2	84
12	benzoyl peroxide	1:4	44
13	benzoyl peroxide	1:8	32

[a]Reaction conditions: **1** (1.67 mg, 6 mM), 2:1 1,4-dioxane/water, 2.18 M HCl overall with various radical initiators heated at 85 °C for 2 h.

radical initiator, gave a 50% conversion to **3** (Table 2, entry 1). Subsequently, several other radical initiators were examined (entries 2−7). Potassium persulfate and *tert*-butyl hydroperoxide led to conversions to **3** in moderate amounts of 17% and 37%, respectively (entries 2 and 5). Hydrogen peroxide (entry 6) gave a very poor conversion to product. No product formation was observed in the absence of a radical initiator. Due to the faster conversion rate and easier UV detection of derivatives of compound **2** compared to AIBN, the former was selected for further reaction optimizations. Experimenting with various ratios of **1**:**2** (entries 8−13) showed that 2 mol equiv of **2** gave the highest conversion to **3** (entry 11). Since lower ratios drastically lowered conversion to **3** (entries 8−10), it is evident that the reaction is not catalytic and **2** takes an active role in the reaction.[40,45] Product formation with use of AIBN as a radical initiator also indicates that the oxygen in the hydroxyl group of the product is likely coming from water, as AIBN does not contain oxygen moieties. To evaluate this hypothesis, $H_2{}^{18}O$ was substituted for H_2O in a reaction using AIBN as a radical initiator and NOBIN with the ^{18}O isotope was formed which was confirmed by mass spectrometry (see Figures S6−S10 in the Supporting

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Information). The same outcome was observed upon usage of **2** as a radical initiator as well.

The effect of eight different acids on the product formation was examined (Table 3). Due to excessive heat formation and evaporation of certain reaction mixtures, the reaction times were limited to 1 h for this study. Use of acetic acid showed no formation of **3** (Table 3, entry 1). When HBr, $HClO_4$, and TFA were used, the conversions to **3** were low (entries 3−5). Use of H_3PO_4 and HCl showed the highest product formations (50% and 46%, entries 7 and 8, respectively). Although the use of H_3PO_4 did lead to a slightly higher conversion to **3** as compared to HCl, the former also produced large amounts of unidentified impurities (up to 40%). Consequently, HCl was chosen for further optimization steps.

Table 3. Optimization of Acid[a]

entry	acid	% conversion of **1** to **3**
1	acetic acid	0
2	methanesulfonic acid	8
3	HBr	10
4	$HClO_4$	11
5	TFA	20
6	HNO_3	29
7	HCl	46
8	H_3PO_4	50

[a]Reaction conditions: **1** (1.67 mg, 6 mM), **2** (2 equiv), 2:1 1,4-dioxane/water with various acids (2.15 M overall) heated at 85 °C for **1 h**.

A series of experiments with varying HCl content (0.65−3.90 M) were also performed to determine the optimal concentration (see Supporting Information Table S1). HCl concentration of 1.30 M provided the highest conversion (94%) to **3** in a 2 h reaction time (entry 3). A steady trend of a decreasing amount of **3** was observed with higher concentrations of acid in the reaction mixture. A reaction mixture of **1** with 2:1 1,4-dioxane/2.0 M HCl (overall) and 2 equiv of **2** was heated at 85 °C and decomposition of reactants and product was observed after 3 h. It is possible that rapid decomposition of **2** after 3 h of reaction led to this outcome.[45] After heating the reaction mixture for several days, multiple impurities were observed in HPLC analysis, yet no traces of BINOL or *S*-NOBIN were found.

A 0.5 mmol scale reaction was performed using **2** as a radical initiator. After workup and purification, **3** was isolated in 65% yield (see Experimental Section for details). When using the above method with H_2O_2 as a radical initiator, little to no product was formed (similar to Table 2 entry 6). A third reaction using the original 0.5 mmol method with **2** as a radical initiator was performed while constantly sparging O_2 in the reaction flask and no product formation was observed. Oxygen, a known free radical scavenger, could quench the free radicals produced by **2** and inhibit the product formation.[46] A similar outcome was observed with the addition of a radical trap (DPPH) to the reaction mixture. This indicates the critical role free radicals play in this reaction.

In order to determine the optimal temperature and reaction time for forming **3**, temperatures ranging from 60 to 175 °C were evaluated. Temperatures below 75 °C showed very little product formation while temperatures above 95 °C showed a large amount of decomposition of reactants and product. An adequate temperature must be provided for an appropriate time to allow for thermal decomposition of **2** to form radicals.[46] Similarly, temperatures higher than 90 °C are above the boiling point of the azeotrope formed by a mixture of 2:1 1,4-dioxane/water, contributing to the short half-life of **2**.[47] The half-life of **2** at 70 and 92 °C is 10 and 1 h, respectively.[48,49] Consequently, temperatures from 75 to 95 °C were further studied to determine the optimal reaction time for the highest possible conversion to product (Table 4). The rate of product formation increased in direct proportion to the increase in temperature. A temperature of 85 °C (entry 3) was determined to be optimal providing a balance of a high amount of product formation in a relatively short reaction time.

Table 4. Optimization of Time and Temperature[a]

entry	time (h)	temp	% conversion of **1** to **3**
1	1.5	75 °C	94
2	2	80 °C	95
3	3	85 °C	98
4	4.5	90 °C	97
5	6.5	95 °C	97

[a]Reaction conditions: **1** (1.67 mg, 6 mM), **2** (2 equiv), 2:1 1,4-dioxane/1.3 M HCl (overall) heated at various temperatures.

With optimal parameters at hand, the reaction was scaled up and optimized for 1 g scale. Similar to past scale-ups, the initial attempts at 1 g scale-up resulted in product decomposition after 3 h at 85 °C. Increasing **2** from 2 to 2.7 equiv and adding it gradually to the flask over 5 h provided 93% conversion to **3** by HPLC analysis after a 6 h reaction time (see Supporting Information). A slow decomposition of the product was observed after 6 h. See the following Experimental Section for the optimized procedure for a 1 g scale reaction. It should be noted that the specific rotation of highly pure *R*-NOBIN, $[\alpha]_D^{24.9}$ = +136 found in this work, is ∼10% higher than previously reported.[50]

While the transformation is formally a Bucherer reaction,[51] the requirement for free radicals would eliminate a fully ionic mechanism. Radical-Bucherer reactions have not been described in detail; however, it is possible that a radical pathway leads to either the imine tautomer or oxidized (semiquinone-like) radical imine of BINAM. These species should undergo hydrolysis under equilibrium and rearomatization to the 2-naphthol group by a mechanism related to the Bucherer reaction. As an example of an oxidative transformation, neutral 9,10-diaminoanthracene is almost instantaneously converted to anthraquinone through a similar yet unknown oxidation/hydrolysis mechanism in air and water.[52] The nonracemization of this process indicates that any redox event, if present, must be isolated to a single naphthalenamine. Furthermore, as no BINOL is observed as a byproduct, the radical process in one naphthalene may be gated by the electronic nature of its neighbor. Further experimentation is required to elucidate this mechanism; what is included here is a hypothetical treatment based on optimization efforts.

In this work, we have documented a successful procedure to directly convert *R*-BINAM to enantiomerically pure *R*-NOBIN in an operationally simple, time-efficient, and cost-effective one-pot procedure. A yield of 70% *R*-NOBIN (>99% ee) was afforded on 1 g scale after workup and purification of product. The product structure and absolute configuration were confirmed using X-ray crystallography among other techniques. This conversion is first of its kind reported for the effective

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synthesis procedures for stereochemically pure NOBIN enantiomers. With optimization, it may be exploited to potentially convert a range of BINAM derivatives into their NOBIN counterparts.

EXPERIMENTAL SECTION

General. All reagents were purchased commercially and were used without further purification. All reactions were performed under Ar. Pressure sealed ampules were used for optimization studies. The following abbreviations were used for NMR multiplicities: s = singlet, d = doublet, dt = doublet of triplet, m = multiplet. For HRMS, APCI-TOF was used. HPLC method used for % conversion analyses: LARIHC CF7-DMP (25 cm × 0.46 cm), mobile phase = 80:20:0.1 heptane/EtOH/butylamine (v/v/v), 2 mL/min, 232 nm, temp = ambient.[53−55] HPLC method used to determine enantiomeric excess: LARIHC CF6-P (15 cm × 0.46 cm, 2.7 μm core−shell), mobile phase = 90:10:0.1 heptane/EtOH/butylamine (v/v/v), 1 mL/min, 232 nm, temp = ambient (~26 °C); $t_{R(S\text{-NOBIN})}$ = 3.83 min, $t_{R(R\text{-NOBIN})}$ = 4.07 min, $t_{R(product)}$ = 4.07 min; R_S = 2.0, α = 1.1 (see Figure S5 in the Supporting Information).[56,57] HPLC columns were provided by AZYP, LLC. (Arlington, TX).

***R*-NOBIN (1 g scale).** *R*-BINAM (1 g or 3.52 mmol) dissolved in 220 mL of 1,4-dioxane, 65 mL of DI (deionized) water, and 47 mL of 12 M HCl (1.7 M overall) was heated at 85 °C for 6 h under Ar. A 2.3 g amount of benzoyl peroxide (9.5 mmol or 2.7 mol equiv) dissolved in 10 mL of 1,4-dioxane was added dropwise (using a syringe pump at constant flow) to the reaction flask over 5 h. Solvents were reduced to ~75% of the proportional amount used in optimization studies. An increase in HCl concentration from 1.3 to 1.7 M showed a better rate of product formation at this scale. The crude mixture was neutralized in an ice bath using drops of saturated NaOH until the pH was ~8. All solvent was evaporated, the crude material was redissolved in 1:1 DI water/EtOAc, and organic products were extracted in EtOAc. *R*-NOBIN was isolated and purified using the Biotage isolera 1 automated system using a step gradient of EtOAc/hexanes and a KP-Sil 50 g column. Product was recrystallized in DCM and washed with hexanes for characterization. The vapor diffusion (vial-in-vial) method with DCM as solvent and hexanes as precipitant was used to form crystals for use in X-ray crystallography. See Supporting Information for details. Product weight 0.7 g (70% yield), >99% ee, white solid, melting point: literature 169 °C, found 170 °C. $[\alpha]_D^{24.9}$ = +136 (c = 1.00, THF). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.74−7.71 (m, 2H), 7.36 (d, J = 8.6 Hz, 1H), 7.25 (dt, J = 6.9 Hz, 1.2 Hz, 1H), 7.19 (dt, J = 6.9, 1.2 Hz, 1H), 7.17 (d, J = 9.2 Hz, 1H), 7.08 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.75 (dt, J = 6.9, 1.7 Hz, 1H), 4.55 (s, 2H) ppm. ^{13}C{^{1}H} NMR (500 MHz, DMSO-d_6) δ 153.4, 144.0, 134.1, 133.7, 129.2, 128.5, 128.2, 128.1, 127.8, 127.1, 126.2, 125.7, 124.2, 123.5, 122.6, 120.8, 118.9, 118.5, 115.0, 111.3 ppm. IR (neat) 3398, 3323, 3213, 3057, 1617, 1509, 1473, 1380, 1273, 1215, 1173, 1145, 818, 752, 662, 424 cm^{-1}. HRMS calculated for $C_{20}H_{15}NO$: 286.1226 ([M + H]$^+$), found 286.1220. Elemental *R*-NOBIN calculated: C, 84.2%; H, 5.3%; N, 4.9%. Commercial standard measured: C, 83.8%; H, 5.1%; N, 4.7%. Product measured: C, 83.1%; H, 5.0%; N, 4.8%.

***R*-NOBIN (0.5 mmol Scale).** *R*-BINAM (0.5 mmol or 142 mg), 42 mL of 1,4-dioxane, 14 mL of DI water, 6.8 mL of 12 M HCl (1.3 M overall), and 2 mol equiv of benzoyl peroxide (1.0 mmol or 250 mg) were heated at 85 °C for 3 h. The crude mixture was neutralized with saturated $NaHCO_3$ until the pH was ~8. All solvent was evaporated, the crude material was redissolved in 1:1 DI water/EtOAc, and organic products were extracted in EtOAc. *R*-NOBIN was isolated using preparative HPLC (column: LARIHC CF6-P 25 cm × 2.12 cm, 95/5 heptane/EtOH, 20 mL/min) to afford a 65% yield. For the reaction with O_2 sparge, O_2 was bubbled in the reaction flask for the duration of the reaction using a gas diffusion tube fitted in a rubber septum.

$H_2{}^{18}O$ Isotope Experiments. *R*-BINAM (2.5 mg or 0.0088 mmol), benzoyl peroxide (4.3 mg or 0.018 mmol), 0.5 mL of 1,4-dioxane (anhydrous), 0.5 mL of 4.0 M HCl in 1,4-dioxane (1.3 M overall), and 0.5 mL of $H_2{}^{18}O$ were heated at 85 °C for 2 h. The product mixture was diluted in ACN and injected in the mass spectrometer (ESI-LIT) for analysis (see Supporting Information). In a separate reaction, 3.1 mg of AIBN (0.019 mmol) were substituted for benzoyl peroxide to study the effect of AIBN as the radical initiator in the reaction.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02663.

CIF X-ray structure file for product (CIF)

Acid concentration optimization (Table S1), NMR spectra, and other characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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