


Tandem approach to NOBIN analogues from arylhydroxylamines and diaryliodonium salts via [3,3]-sigmatropic rearrangement†

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Herein, we present a transition-metal free direct *O*-arylation of arylhydroxylamines employing diaryliodonium salts as arylation reagents to form transient *N,O*-diarylhydroxylamines that could subsequently undergo [3,3]-sigmatropic rearrangement and re-aromatization to afford structurally diverse NOBIN analogs in good to excellent yields under mild conditions.

The axially chiral biaryls are privileged structures in organic chemistry due to their wide appearance in natural products, pharmaceuticals and materials science.¹ Over the past two decades, 1,1'-bi-2-naphthol (BINOL), 1,1'-binaphthyl-2,2'-diamine (BINAM) and 2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN) and their analogs were extensively applied as catalysts or ligands in the field of asymmetric catalysis.² Therefore, great effort has been made to develop synthetic strategies for the construction of axially chiral biaryls from diverse starting materials and numerous methods have been developed.^{1*h*,3} Compared to the relatively well established asymmetric synthetic routes to BINOL-type biaryls from achiral precursors,⁴ only limited enantioselective approaches to NOBIN-analogues were reported before 2016. Transition metal-catalyzed traditional Ar–Ar cross-coupling (*e.g.* Suzuki reaction) is one of the most widely used strategies to prepare biaryls, which need the prefunctionalization of both coupling partners, and it is difficult to construct unprotected

nitroarenes with aryl-Grignard reagents ($X = O$, $Y = N(MgBr)$, Scheme 1(II))⁸ and chiral Brønsted acid catalyzed benzidine rearrangement of N,N' -diarylhydrazines ($X, Y = NH$, Scheme 1(I)).^{3a,b}

Recently, we developed a copper-catalyzed tandem protocol, including O -vinylation, [3,3]-sigmatropic rearrangement, intramolecular cyclization and re-aromatization, for the synthesis of indoles from readily available arylhydroxylamines **1** and vinyliodonium salts **2** under mild conditions (Scheme 1(II)).⁹ Naturally, we were intrigued by the possibility of employing diaryliodonium salts **5** to react with arylhydroxylamines **1** to prepare racemic NOBIN-type biaryls through a transient N,O -diarylhydroxylamine intermediate **6**,¹⁰ which could undergo a similar Bartoli-type [3,3]-rearrangement and rearomatization (Scheme 1(III)).^{8,11} Diaryliodonium salts are an environmentally benign electrophilic arylating reagent with high reactivity, low toxicity, and air and moisture stability.¹² Inspired by the aforementioned elegant strategies to NOBIN analogues, we herein describe a TM-free cascade protocol to structurally diverse non- C_2 symmetrical biaryls using diaryliodonium salts as arylating reagents in combination with an NHC-catalyzed kinetic resolution process to produce enantiopure NOBIN and its analogues (Scheme 1(III)).

We start our investigation by choosing N -hydroxy- N -(naphthalen-2-yl)benzamide **1a** and diphenyl- λ^3 -iodanyl trifluoromethane-sulfonate **5a** as model substrates to test our hypothesis. After a series of screenings of bases, catalysts and anions of iodonium salts, we were very pleased to find that the combination of 1.2 equivalents of diphenyliodonium tetrafluoroborate with 1.5 equivalents of $NaHCO_3$ in the absence of metal catalysts in 1,2-dichloroethane at 35 °C under N_2 is the optimal reaction conditions for this tandem transformation and up to 90% yield of the desired biaryl product can be obtained (for detailed optimization study, see the ESI†).

With the optimized reaction conditions in hand, we next explore the scope and limitation of this transformation. To our delight, this TM-free tandem approach has a broad range of arylhydroxylamines and diaryliodonium salts, providing access to a diverse array of highly functionalized biaryl motifs (Table 1). The desired racemic NOBIN-type products **7** were obtained in moderate to excellent yields (up to 97%) with excellent regioselectivity. Various substituents on the naphthylhydroxylamine moiety as well as diaryliodonium salt functionality were well tolerated under the standard conditions. It is noteworthy that a series of multiple halogens or trifluoromethyl substituted biaryl amino alcohols, which are difficult to access through conventional approaches, can be efficiently prepared by this methodology (Table 1, entries 13–17 and 41–44). This protocol is amenable not only for naphthyl-naphthyl NOBIN-type products but also for naphthyl-phenyl non- C_2 -symmetrical biaryls (Table 1, entries 18–20, 34–40 and 21–33, 41–44). Phenylhydroxylamines were also applicable to this transformation albeit with relatively lower yields (Table 1, entries 32 and 33). The structure of the product was unambiguously confirmed by the single crystal X-ray diffraction study of compound **7h** (Table 1, entry 8).

With these structurally diverse racemic biaryls in hand, we next turned our attention to exploring various catalytic strategies

Table 1 Substrate scope of racemic NOBIN-type biaryls^{ab}

Reaction scheme: $1 + 5 \xrightarrow{NaHCO_3 (1.5 \text{ equiv}), DCE, 35-50^\circ C} 7$

Compounds 5: Type A, Type B, Type C

Yields and substituents for Type A (1):

- (1)^a **7a**, $X = H$, 88%
- (2)^a **7b**, $X = F$, 54%
- (3)^a **7c**, $X = Cl$, 56%
- (4)^a **7d**, $X = Br$, 50%
- (5)^a **7e**, $X = CN$, 74%
- (6)^a **7f**, $X = SO_2Me$, 95%
- (7)^a **7g**, $X = CO_2Me$, 53%
- (8)^a **7h**, $X = CF_3$, 88%
- (9)^a **7i**, $X = CMe_3$, 50%
- (10)^a **7j**, $X = Me$, 59%

Yields and substituents for Type B (1):

- (11)^a **7k**, $X = Br$, 56%
- (12)^a **7l**, $X = Me$, 36%
- (13)^a **7m**, $X = Br$, 56%
- (14)^a **7n**, $X = Cl$, 59%
- (15)^a **7o**, $X = Br$, 48%
- (16)^a **7p**, $X = CF_3$, 57%

Yields and substituents for Type C (1):

- (17)^a **7q**, $X = Br$, 56%
- (18)^a **7r**, $X = H$, 1%
- (19)^a **7s**, $X = Br$, 69%
- (20)^a **7t**, $X = Br$, 88%
- (21)^a **7u**, $X = H$, 62%
- (22)^a **7v**, $X = Ph$, 52%
- (23)^a **7w**, $X = Me$, 72%
- (24)^a **7x**, $X = OBn$, 43%
- (25)^a **7y**, $X = Br$, 37%
- (26)^a **7z**, $X = OMe$, 49%
- (27)^a **7aa**, $X = OBn$, 64%
- (28)^a **7ab**, $X = Br$, 70%
- (29)^a **7ac**, $X = H$, 90%
- (30)^a **7ad**, $X = F$, 85%
- (31)^a **7ae**, $X = OMe$, 74%
- (32)^a **7af**, $X = Me$, 37%
- (33)^a **7ag**, $X = Cl$, 29%
- (34)^a **7ah**, $X = OMe$, 35%
- (35)^a **7ai**, $X = OBn$, 43%
- (36)^a **7aj**, $X = Br$, 37%
- (37)^a **7ak**, 68%
- (38)^a **7al**, 58%
- (39)^a **7am**, 52%

^a Reaction conditions: **1** (0.2 mmol), **5** (0.24 mmol), $NaHCO_3$ (0.30 mmol), DCE (1 mL) at 35–50 °C under N_2 . ^b Isolated yields. Bn = benzyl. ^c Compound **5** of Type A was used. ^d Compound **5** of Type B was used. ^e Compound **5** of Type C was used.

for the resolution of **7**. These strategies included a chiral phase transfer catalyst mediated alkylation of the $O-H$ bond,¹³ a cinchona alkaloid-derived chiral amine catalyzed N -alkylation with MBH carbonate¹⁴ and an NHC-catalyzed acylation of the OH group.¹⁵ Inspired by Zhao^{15a,c} and Wang's^{15b} elegant work and after a series of screenings, the NHC-catalyzed O -acylation of **7r** using isovaleraldehyde **8** in the presence of DQ (3,3',5,5'-tetra-*tert*-butyl-[1,1'-bi(cyclohexylidene)]-2,2',5,5'-tetraene-4,4'-dione) as an oxidant at room temperature proved to be the most

Table 2 NHC-catalyzed kinetic resolution of racemic NOBIN-type biaryls^{abc}

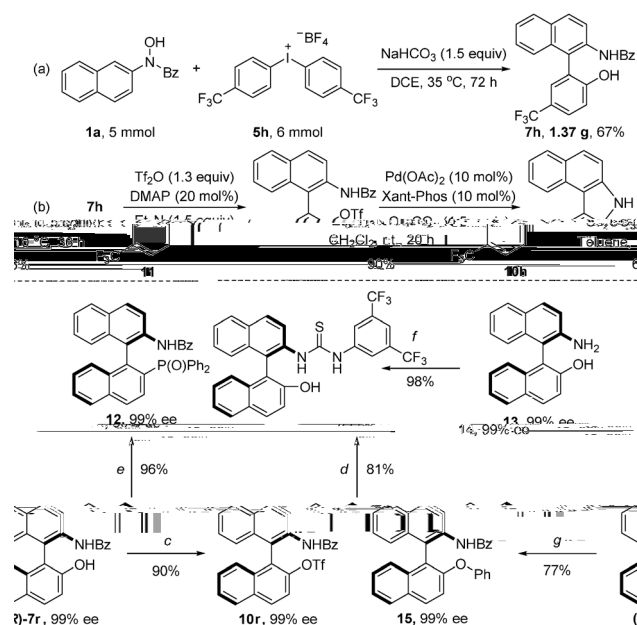
Substrate	Yield (%)	ee (%)	S
(±)-7a	45%	95% ee	48
(R)-7a	45%	95% ee	48
(R)-7b	43%	90% ee	44
(R)-7c	44%	95% ee	47
(R)-7d	43%	95% ee	46
(R)-7e	45%	95% ee	44
(R)-7f	45%	95% ee	44
(R)-7g	45%	95% ee	44
(R)-7h	45%	95% ee	44

^a Reaction conditions: **7** (0.05 mmol), isovaleraldehyde **8** (0.2 mmol), K₂CO₃ (0.1 mmol), DQ (0.1 mmol), NHC1 (10 mol%), Solvent (2 mL) at 25 °C. ^b Yields of isolated products. ^c Conv. = ee_{(R)-7}/(ee₉ + ee_{(R)-7}); S = ln[(1 - conv.)(1 - ee_{(R)-7})]/ln[(1 - conv.)(1 + ee_{(R)-7})].

promising and resulted in the best enantioselectivity. (For a detailed optimization study of kinetic resolution, see the ESI.†) Encouraged by the successful resolution of **7r**, we then planned to investigate the generality of this NHC-catalyzed kinetic resolution strategy. We were very pleased to find that this catalytic system was applicable to a wide range of substrate

scopes and most of those racemic NOBIN-type biaryls we made can be recovered in >90% ee with 39–48% isolated yield (Table 2). Both naphthyl-naphthyl NOBIN-type products and naphthyl-phenyl non-C₂-symmetrical biaryls with various substituents on the two aromatic rings can be efficiently resolved with up to 133 selectivity. Notably, the absolute configuration of the enantiopure biaryls was determined by the single crystal X-ray analysis of recovered **7o** (Table 2, entry 8).

To demonstrate the synthetic practicability of this TM-free cascade protocol, a gram-scale synthesis of **7h** was carried out under standard conditions (Scheme 2a). We delightfully found that the gram-scale reaction proceeded smoothly to afford 1.37 grams of **7h** in 67% yield and excellent regioselectivity. Moreover, the biaryl triflate **10h**, which is derived from **7h** in excellent yield,¹⁶ can be converted into carbazole **11** in moderate yield through a palladium-catalyzed intramolecular amination/cyclization¹⁷ (Scheme 2b). To further investigate the synthetic utility of the chiral NOBIN products, (*R*)-**7r** was elaborated as shown in Scheme 2. Treatment of (*R*)-**7r** with (CF₃SO₂)₂O in the presence of triethylamine gives its triflate derivative **10r** in 90% yield¹⁶ (Scheme 2c). The coupling reaction of **10r** with diphenylphosphine oxide proceeded efficiently in the presence of Pd(OAc)₂/dppp (dppp = 1,3-bis(diphenylphosphino)propane) and diisopropylethylamine to give (*R*)-*N*-(2'-(diphenylphosphoryl)-[1,1'-binaphthalen]-2-yl)benzamide **12** in 81% yield and 99% ee^{2a} (Scheme 2d). (*R*)-NOBIN **13**, which is derived from the deprotection of amine in the presence of potassium hydroxide in 96% yield and 99% ee,¹⁸ can be converted into the corresponding thiourea **14** in 98% yield and 99% ee in the presence of isothiocyanate¹⁹ (Scheme 2e and f). In addition, (*R*)-**7r** can be



Scheme 2 Grams scale reaction and synthetic applications of the biaryl products. (c) Tf₂O, DMAP, Et₃N, CH₂Cl₂, r.t., 20 h. (d) HP(O)Ph₂, Pd(OAc)₂, dppp, iPr₂NEt, DMSO, 100 °C, 24 h. (e) KOH, EtOH, 100 °C, 18 h. (f) Isothiocyanate, THF, 30 °C, 12 h. (g) Cu(OAc)₂, PhB(OH)₂, Et₃N, 4 Å Molecular Sieves, Ethyl Acetate, 30 °C, 12 h.

further *O*-arylated with arylboronic acid *via* a Chan–Lam coupling reaction to generate **15** in 77% yield and 99% ee²⁰ (Scheme 2g).

In conclusion, a TM-free cascade protocol from readily available arylhydroxylamines and diaryliodonium salts for the straightforward construction of structurally diverse non-C₂ symmetrical NOBIN-type biaryls, was developed. A NHC-catalyzed kinetic resolution was also successfully achieved for the preparation of enantiopure NOBIN analogs under mild conditions. This transformation is scalable and the resulting biaryls can be further transformed into brand new heterocycles and atropoisometric biaryl compounds. Further investigation of the utility of the chiral biaryls in asymmetric catalysis is currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

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