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Practical Organocatalytic Synthesis of Non-C₂-Symmetrical Atropoisomeric BINOL/NOBIN-Type Functionalized Biaryls**

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Hindered rotation about the C-C bond in biaryl compounds renders the biaryl axis stereogenic, which is a key structural motif in a large number of natural products, pharmaceuticals, chiral auxiliaries, ligands and catalysts (Figure 1). The magnitude of this

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barrier of rotation is determined by both the size and number of substituents at the ortho positions flanking the aryl-aryl bond [1]

Among natural products it is common that opposite biaryl enantiomers, called atropoisomers, display completely different biological profiles (e.g., gossypol, Figure 1)^[1c] and recently it was recognized that controlling the chirality of unsymmetrical biaryl structures will have enormous implications in the future development of pharmaceuticals.^[2] During the past two decades, both C₂- and non-C₂-symmetrical axially chiral biaryl compounds^[1a-c] (e.g., BINAP, BINOL, BINAM, NOBIN and their derivatives, Figure 1) have played key roles as ligands for transition-metals in the development of catalytic enantioselective transformations.^[3] Functionalized biaryls have also been referred to as “*privileged chiral catalysts*”, a term that was coined by Jacobsen,^[3j] because these ligands result in good enantioselectivity over many different (i.e., mechanistically unrelated) reactions.

A number of synthetic approaches have been developed for the construction of axially chiral biaryl compounds (Figure 2).^[4] However, there are a number of biaryl linkages that remain exceedingly difficult to construct in an atom- and step-economical fashion. In particular, 2,2'-di-heteroatom substituted non-C₂-symmetrical 1,1'-biaryls (e.g., the highly functionalized 2,2'-aminohydroxy-1,1'-biaryl motif found in TMC-95A and Streptonigrin, Figure 1) have not been readily accessible until recently.^[5] However, serious challenges remain especially with regard to achieving diverse substitution patterns on the biaryl scaffold. Synthetic access is even more limited for non-C₂-symmetrical but configurationally stable biaryldiols (e.g., 2,2'-dihydroxy-1,1'-biaryl motif found in certain chiral phosphoric acids) as no general methods are currently available for their preparation.^[6] The scarcity of reliable methods is surprising as these atropisomeric but non-C₂-symmetrical biaryldiols have been shown to be excellent ligands or catalysts in many catalytic reactions, especially in those where the C₂-symmetrical scaffolds were found to be ineffective.^[3b]

Some of the most widely used aryl-aryl C-C bond-forming strategies include: (1) transition metal-catalyzed aryl-aryl *traditional cross-coupling*^[7] that requires pre-functionalization of both coupling partners (e.g., Negishi, Stille, Kumada and Suzuki reactions, Figure 2, **A**), (2) *oxidative direct arylation*^[4e, 8] that requires the pre-functionalization of just one of the coupling partners (Figure 2, **B**) and (3) *dehydrogenative cross-coupling*^[9] that does not require either coupling partner to be pre-functionalized (Figure 2, **C**); (4) *TM-free direct arylation* that takes place between *o*-halogen-substituted nitroarenes and aryl Grignard reagents^[5] to afford 2-amino-2'-hydroxy-1,1'-biaryls (i.e., NOBIN-type ligands) under very mild conditions via the [3,3]-sigmatropic rearrangement of *N,O*-biarylhydroxylamines as intermediates (Figure 2, **D**) and (5) the chiral phosphoric acid-catalyzed [3,3]-rearrangement of *N,N'*-diarylhydrazines to afford substituted BINAMs (Figure 2, **E**).^[10]

As part of an ongoing program in our group to develop new and practical TM-free direct arylation methods for the preparation of highly functionalized symmetrical and unsymmetrical biaryls^[5, 10b], we became intrigued by the possibility of using quinone and iminoquinone monoacetals^[11] as aryating agents to access both BINOL/NOBIN-type of functionalized biaryls, that are atropisomeric but non-C₂-symmetrical, from phenols and

naphthols under organocatalytic conditions (Figure 2). The coupling of quinone monoacetals with alkoxyarenes has only been demonstrated in the presence of solid acids such as montmorillonite (MT) clay.^[12] Surprisingly, traditional Brønsted or Lewis acids were found to be completely ineffective in these studies. We argued that if quinone monoacetals (**1**) were reacted with unprotected naphthols (**2**) in the presence of a strong Brønsted acid catalyst, an acetal exchange would afford the corresponding mixed-acetals (**3**, Scheme 1).

The mixed-acetal (**3**) then would undergo a $[3,3]$ -sigmatropic rearrangement (i.e., Claisen rearrangement) to afford a dearomatized intermediate (**4**) which, upon rapid re-aromatization, is expected to furnish the corresponding functionalized biaryls (**5**).^[13]

In order to test the hypothesis outlined above, we began to look for suitable combinations of strong organic acids (i.e., Brønsted acids) and solvents (Table 1). We chose quinone monoacetal **1a** and 2-naphthol **2a** as coupling partners. In the highly polar solvent of 2,2,2-trifluoroethanol (TFE), very strong Brønsted acids (e.g., triflic acid, methansulfonic acid, hydrochloric acid; Table 1, entries 1-3) gave poor results, however, the somewhat weaker acids such as *p*-toluenesulfonic acid, trifluoroacetic acid and diphenylphosphoric acid (i.e., *p*-TSA, TFA & DPA) furnished the desired functionalized biaryl product **5a** in moderate to excellent yields at room temperature (Table 1, entries 4-6). In order to achieve the highest isolated yield of **5a** in the shortest possible time we found that the use of 2 equivalents of **2a** and 20 mol% of the organic acid catalyst were necessary (Table 1, entries 6-10). When the weakly polar solvent dichloromethane was utilized along with catalytic amounts of DPA or TFA, the direct arylation of **2a** did not proceed at 25 °C, however, moderate yield of **5a** was obtained at reflux temperature (Table 1, entries 11-14). After screening a series of different combinations of acid and solvent at various temperatures, we found that the combination of TFA and toluene at 100 °C afforded **5a** in 84% isolated yield in 16 hours (Table 1, entry 17; for a more detailed optimization study, see the Supporting Information).

With the optimization results in hand, we selected two suitable reaction conditions (**A**: 20 mol% of TFA in toluene at 100 °C and **B**: 20 mol% of DPA in TFE at 25 °C) and initiated an extensive study to determine the scope of substrates. We began with diversely substituted 2-naphthols (Table 2, entries 1-8) that range from strongly electron rich to weakly electron-poor rings. For this series reaction condition **A** seemed to work the best as isolated yields of the product biaryldiols ranged between good to excellent. Only in the case of products **5a**, **5e** & **5i** (entries 1, 5 & 9) was reaction condition **B** superior. To our delight, several of these reactions could be readily scaled up; biaryldiol **5c** was prepared on a 26 gram scale (starting from 98 mmols of **1a**) which is particularly well-suited for ligand/catalyst synthesis. The structure of biaryl **5c** was confirmed using single crystal X-ray crystallography.

Varying the structure of the quinone monoacetal coupling partner (entries 9-12) did not cause any issues and, remarkably an electron-poor 2-naphthol could be coupled with an electron poor quinone monoacetal to afford functionalized biaryldiol **5j** (entry 10). The presence of the Br substituent in the 6-position will allow further elaboration of the naphthalene nucleus (e.g., via TM-catalyzed cross-coupling reactions). When 1-naphthol was used in the transformation (entries 13 & 14), we were able to control the regioselectivity of the direct arylation reaction (i.e., 2- versus 4-position) by switching between conditions **A**

and **B**. Monocyclic phenols (entries 15 -19) were found to be equally suitable substrates for this transformation as substituted 1- or 2-naphthols, allowing the preparation of biaryldiols that have hindered rotation about their chiral axis (i.e., configurationally stable functionalized biaryls).

Finally, 2,3-dihydroxynaphthalene can be coupled twice with quinone monoacetal **1a** to afford a functionalized terphenyl **5s** in good isolated yield (Table 2, entry 20). Intriguingly, only the *anti* diastereomer was obtained (i.e., racemic form) while the *syn* diastereomer (i.e., *meso* form) was not observed. This structural assignment was confirmed by subjecting the exhaustively *O*-methylated derivative of **5s** to single crystal X-ray diffraction. Nearly all of the biaryldiols shown in Table 2 are new compounds/structures, previously not accessible in an operationally simple and scalable process.

Next, we prepared three iminoquinone monoacetals (**6a-c**) and were able to successfully couple these with nine different naphthols (Table 3, entries 21-29 & 32-39) and four different phenols (entries 30, 31, 40 & 41) under the previously optimized reactions conditions **A** or **B**. The presence of the sulfonyl group (Ts = *p*-toluenesulfonyl & Ms = methanesulfonyl) on the nitrogen atom was necessary to impart sufficient reactivity for the system. The resulting *N*-sulfonyl substituted 2-amino-2'-hydroxy-1,1'-biaryls are of the NOBIN-type and completely novel structures. The *N*-sulfonyl group can be efficiently removed using a previously published protocol.^[14]

Naturally, we also briefly explored the possibility of using chiral BINOL-derived phosphoric acids to catalyze the coupling of **1a** with **2a** to afford **5a** in an enantiomerically enriched form. After testing six popular chiral phosphoric acid catalysts in toluene (10 mol% catalyst loading) between room temperature and 50°C, we found that despite achieving moderate to good isolated yields of **5a** (24-72%), the level of enantio-induction was very poor (3-10% *ee*; see details in the SI). Studies are currently ongoing to develop a catalytic enantioselective version of this coupling reaction.

In order to examine the mechanistic feasibility of the proposed mixed acetal/[3,3]-sigmatropic rearrangement sequence (outlined in Scheme 1), we conducted M06-2X density functional calculations on a model system^[15] (see SI for details).^{[16] [17] [18]} The results of these calculations indicate that the mixed acetal (**3**)^[19] can indeed undergo a low-barrier TFA-catalyzed [3,3]-rearrangement ($H^\ddagger < 10$ kcal/mol).^[20] Subsequent re-aromatization after this rearrangement gives rise to the corresponding biaryl product. Importantly, this mixed acetal/[3,3]-sigmatropic rearrangement reaction pathway is consistent with the nonreactivity of 2-methoxynaphthalene since it cannot generate the mixed acetal intermediate (Figure 3).

We also briefly examined a limited number of alternative reaction pathways. For example, we tested the possibility that 2-naphthol nucleophilically captures the oxocarbenium intermediate (**10**, Figure 3) that is required for acetal group exchange. This pathway was found to have a barrier that is close to the barrier height for the [3,3]-sigmatropic rearrangement. However, this reaction pathway cannot account for the non-reactivity of 2-methoxynaphthalene. We also examined the possibility that there could be TFA-catalyzed C-

C bond formation between 2-naphthol and the quinone monoacetal in an S_N2' type reaction pathway. However, extensive transition state searching failed to locate a concerted S_N2' transition state.

While nearly all biaryl products reported in this study can be rationalized by a mixed acetal/[3,3]-sigmatropic rearrangement pathway, it is important to note that the formation of biaryl **5m'** (entry 14, Table 2) cannot. Rather, biaryl **5m'** could be formed by either a [3,5]-sigmatropic shift or an S_N2' type mechanism (see the SI for details). Gratifyingly we only observed mono-arylated products. A comprehensive experimental and computational mechanistic study is currently underway.

In summary, we have developed a practical, external oxidant-free, organocatalytic direct arylation protocol for the regioselective preparation of 1,1'-linked functionalized biaryls. The products are non- C_2 -symmetrical atropisomeric biaryldiols (i.e., BINOL-type) and aminohydroxy biaryls (i.e., NOBIN-type), most of which are *novel structures reported here for the first time*. DFT calculations revealed that the mechanism most likely involves a tandem mixed-acetal formation/[3,3]-rearrangement sequence. We anticipate that this transformation may serve as a prototype for related powerful transformations that build molecular complexity rapidly, with exceptional step-economy and in an environmentally friendly fashion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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We were unable to isolate mixed acetal intermediates from the reaction mixtures. This is not surprising given the highly acid-sensitive nature of quinone monoacetals.

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Figure 1.
The axially chiral functionalized biaryl motif in natural products, ligands and catalysts.

Figure 2.

Various methods for the construction of aryl-aryl bonds, including our organocatalytic direct arylation protocol to access non- C_2 -symmetrical BINOL/NOBIN-type functionalized biaryl systems.

Scheme 1.

Proposed direct arylation of 2-naphthols via Brønsted acid-catalyzed tandem mixed acetal formation/[3,3]-sigmatropic rearrangement sequence.

Figure 3.

Formation of a mixed-acetal intermediate is not possible with 2-methoxy naphthalene (**9**), thus coupling with **1** does not occur. Unprotected naphthol (**2**) undergoes smooth arylation to afford biaryl diol (**5a**).

Table 1

Optimization of conditions for **1a** + **2a** → **5a**.

Entry ^[a]	Acid	Solvent	Temp. (°C)	Time (h)	Yield ^[b] (%)
1	TfOH	CF ₃ CH ₂ OH	25	16	< 5
2	MsOH	CF ₃ CH ₂ OH	25	16	< 5
3	HCl	CF ₃ CH ₂ OH	25	16	48
4	TsOH·H ₂ O	CF ₃ CH ₂ OH	25	16	52
5	TFA	CF ₃ CH ₂ OH	25	16	59
6	(PhO) ₂ PO ₂ H	CF ₃ CH ₂ OH	25	16	85
7 ^[c]	(PhO) ₂ PO ₂ H	CF ₃ CH ₂ OH	25	18	75
8 ^[d]	(PhO) ₂ PO ₂ H	CF ₃ CH ₂ OH	25	18	65
9 ^[e]	(PhO) ₂ PO ₂ H	CF ₃ CH ₂ OH	25	24	83
10 ^[f]	(PhO) ₂ PO ₂ H	CF ₃ CH ₂ OH	25	24	78
11	(PhO) ₂ PO ₂ H	CH ₂ Cl ₂	25	16	N.R. ^[g]
12	(PhO) ₂ PO ₂ H	CH ₂ Cl ₂	reflux	16	42
13	TFA	CH ₂ Cl ₂	25	24	N.R.
14	TFA	CH ₂ Cl ₂	reflux	24	60
15	TFA	Toluene	25	16	N.R.
16	TFA	Toluene	50	18	64
17	TFA	Toluene	100	16	84

^[a] **1a** (0.2 mmol), **2a** (2.0 equiv), 20 mol% of acid and 2 mL solvent were employed – unreacted **2a** can be recovered via flash chromatography and reused

^[b] Isolated yield

^[c] 1.5 equiv of **2a** was used

^[d] 1.2 equiv of **2a** was used

^[e] 10 mol% of acid was used

^[f] 5 mol% of acid was used

^[g] N.R. = No Reaction.

Table 2

Preparation of non- C_2 -symmetrical atropoisomeric 2,2'-dihydroxy-1,1'-biaryls (i.e., BINOL-type) from naphthols and phenols (**5a-r**).

Structure of Non- C_2 -Symmetrical Biaryldiols (Entry) ^[a] Compound #, Isolated Yield (%) ^[b]	
 (1): 5a A, 84%; B, 85%	 A, 65%; B, 12%
 A, 76%; B, 48% (98 mmol scale)	 m.p. = 217-218 °C
 A, 75%	 B, 70%
 A, 60%; B, 55%	 A, 70%; B, 60% (1 mmol scale)
 A, 90% yield	 A, 15%; B, 68% yield (5 mmol)
 A, 72%; B, 60% (40 mmol scale)	 A, 64%
 A, 70%	 A, 69%
 B, 80%	 A, 54%
 A, 65%	 A, 65%
 A, 75%	 A, 69%
 A, 54% (only the anti diastereomer) A, 50% (8 mmol scale)	 m.p. = 232-235 °C

[a] Reactions were performed on 0.2 or 0.3 mmol scale (0.1 M solution); [b] Isolated yield after column chromatography.

Table 3

Preparation of non- C_2 -symmetrical atropisomeric 2-amino-2'-hydroxy-1,1'-biaryls (i.e., NOBIN-type) from naphthols and phenols (**7a-u**).

[a] Reactions were performed on 0.2 or 0.3 mmol scale (0.1 M solution); [b] Isolated yield after column chromatography.