Biaryl Synthesis **Hot Paper**

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Practical Organocatalytic Synthesis of Functionalized Non-C_2-Symmetrical Atropisomeric Biaryls

*Hongyin Gao+, Qing-Long Xu+, Craig Keene, Muhammed Yousufuddin, Daniel H. Ess, and László Kürti**

Abstract: *An organic acid catalyzed direct arylation of aromatic C(sp^2)−H bonds in phenols and naphthols for the preparation of 1,1′-linked functionalized biaryls was developed. The products are non-C_2-symmetrical, atropoisomeric, and represent previously untapped chemical space. Overall this transformation is operationally simple, does not require an external oxidant, is readily scaled up (up to 98 mmol), and the structurally diverse 2,2′-dihydroxy biaryl (i.e., BINOL-type), as well as 2-amino-2′-hydroxy products (i.e., NOBIN-type) are formed with complete regioselectivity. Density-functional calculations suggest that the quinone and imino-quinone monoacetal coupling partners are exclusively arylated at their α-position by an asynchronous [3,3]-sigmatropic rearrangement of a mixed acetal species which is formed in situ under the reaction conditions.*

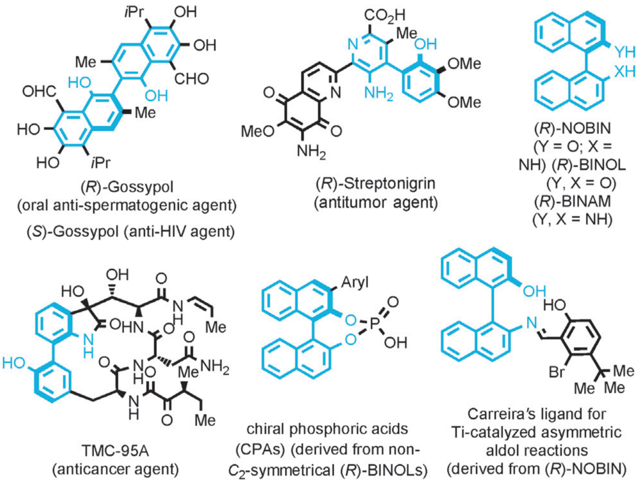

Figure 1. The axially chiral functionalized biaryl motif in natural products, ligands, and catalysts.

Hindered rotation about the C−C bond in biaryl compounds renders the biaryl axis stereogenic, and is a key structural motif in a large number of natural products, pharmaceuticals, chiral auxiliaries, ligands, and catalysts (Figure 1). The magnitude of this 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 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 can have enormous implications in the future development of pharmaceuticals.[2] During the past two decades, both C_2- and non-C_2-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 for 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-C_2-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-C_2-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 atropoisomeric but non-C_2-symmetrical biaryldiols have been shown to be excellent ligands or catalysts in many catalytic reactions, especially in those where the C_2-symmetrical scaffolds were found to be ineffective.[3b]

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[*] Dr. H. Gao,[+] Prof. Dr. Q.-L. Xu,[$] [+] C. Keene, Prof. Dr. L. Kürti
Department of Chemistry, Rice University
BioScience Research Collaborative
6500 Main Street, Rm 380, Houston, TX 77030 (USA)
E-mail: kurti.laszlo@rice.edu

Dr. M. Yousufuddin
Life and Health Sciences Department
The University of North Texas at Dallas, Dallas, TX 75241 (USA)

Prof. Dr. D. H. Ess
Department of Chemistry and Biochemistry
Brigham Young University, Provo, UT 84602 (USA)

[$] Current address: Jiangsu Key Laboratory of Drug Discovery for Metabolic Disease and State Key Laboratory of Natural Medicines
China Pharmaceutical University
24 Tongjia Xiang, Nanjing 210009 (P.R. China)

[+] These authors contributed equally to this work.

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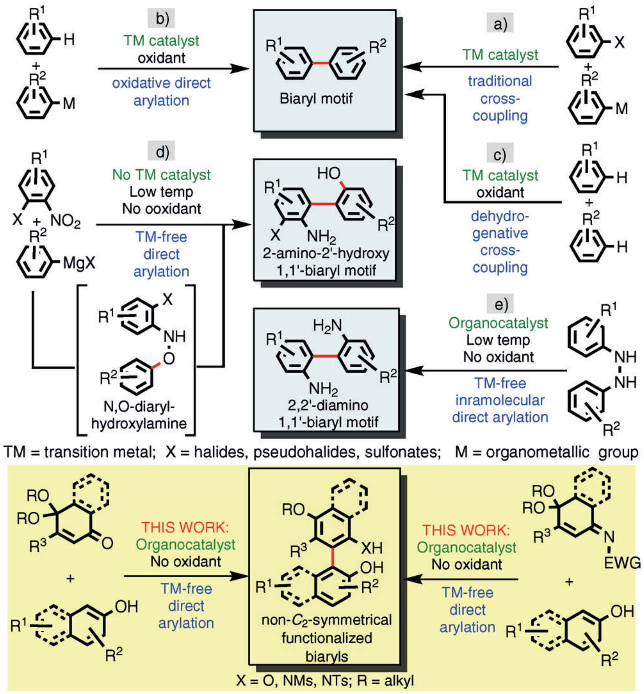
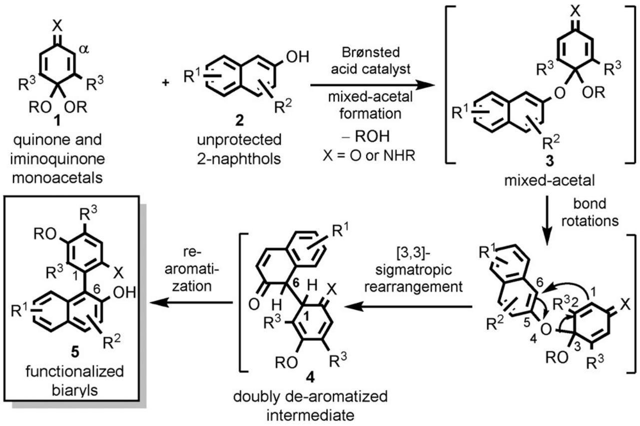


Figure 2. Various methods for the construction of aryl–aryl bonds, including our organocatalytic direct arylation protocol to access non-C_2-symmetrical BINOL/NOBIN-type functionalized biaryl systems. EWG = eletron-wihdrawing group.

Some of the most widely used aryl–aryl C–C bond-forming strategies include: 1) transition-metal-catalyzed traditional aryl–aryl cross-coupling,[7] which requires pre-functionalization of both coupling partners (e.g., Negishi, Stille, Kumada, and Suzuki reactions; Figure 2 a), 2) oxidative direct arylation,[4e,8] which requires the pre-functionalization of just one of the coupling partners (Figure 2 b), and 3) dehydrogenative cross-coupling,[9] which does not require either coupling partner to be pre-functionalized (Figure 2 c); 4) TM-free direct arylation which takes place between *ortho*-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 reaction conditions by 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 imino-quinone monoacetals[11] as arylating agents to access both BINOL/NOBIN-type of functionalized biaryls, which are atropoisomeric but non-C_2-symmetrical, from phenols and naphthols under organocatalytic conditions (Figure 2). The coupling of quinone monoacteals 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]

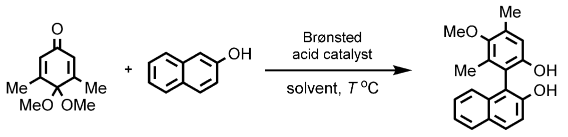


Scheme 1. Proposed direct arylation of 2-naphthols by Brønsted acid catalyzed tandem mixed-acetal formation/[3,3]-sigmatropic rearrangement sequence.

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 the quinone monoacetal **1 a** and 2-naphthol (**2 a**) 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; entries 1–3) gave poor results, however, the somewhat weaker acids such as *p*-toluenesulfonic acid (TSA), trifluoroacetic acid (TFA), and diphenylphosphoric acid (DPA) furnished the desired functionalized biaryl product **5 a** in moderate to excellent yields at room temperature (entries 4–6). To achieve the highest yield of isolated **5 a** in the shortest possible time we found that the use of 2 equivalents of **2 a** and 20 mol % of the organic acid catalyst were necessary (entries 6–10). When the weakly polar solvent dichloromethane was utilized along with catalytic amounts of either DPA or TFA, the direct arylation of **2 a** did not proceed at 25 °C. However, moderate yield of **5 a** was obtained at reflux (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 **5 a** in 84 % yield after 16 hours (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) ranging from strongly electron-rich to weakly electron-poor rings. For this series the reaction conditions A seemed to work the best as yields of the isolated

Table 1: Optimization of reaction conditions for the model reaction.

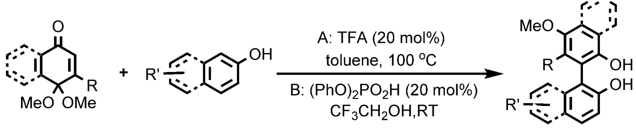


1a **2a** **5a**

Entry[a]	Acid	Solvent	T [°C]	t [h]	Yield [%][b]
1	TfOH	CF_3CH_2OH	25	16	< 5
2	MsOH	CF_3CH_2OH	25	16	< 5
3	HCl	CF_3CH_2OH	25	16	48
4	$TsOH\cdot H_2O$	CF_3CH_2OH	25	16	52
5	TFA	CF_3CH_2OH	25	16	59
6	$(PhO)_2PO_2H$	CF_3CH_2OH	25	16	85
7[c]	$(PhO)_2PO_2H$	CF_3CH_2OH	25	18	75
8[d]	$(PhO)_2PO_2H$	CF_3CH_2OH	25	18	65
9[e]	$(PhO)_2PO_2H$	CF_3CH_2OH	25	24	83
10[f]	$(PhO)_2PO_2H$	CF_3CH_2OH	25	24	78
11	$(PhO)_2PO_2H$	CH_2Cl_2	25	16	n.r.
12	$(PhO)_2PO_2H$	CH_2Cl_2	reflux	16	42
13	TFA	CH_2Cl_2	25	24	n.r.
14	TFA	CH_2Cl_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 by flash chromatography and reused. [b] Yield of the isolated product. [c] 1.5 equiv of **2a** used. [d] 1.2 equiv of **2a** used. [e] 10 mol% of acid used. [f] 5 mol% of acid used. n.r. = no reaction, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

Table 2: Preparation of non-C_2-symmetrical atropoisomeric 2,2′-dihydroxy-1,1′-biaryls (i.e., BINOL-type) from naphthols and phenols.[a,b,c]



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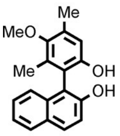
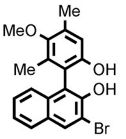
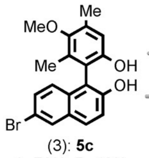


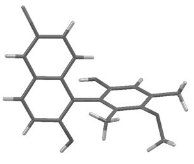
(1): **5a**
A, 84%; B, 85%



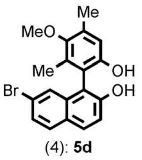
(2): **5b**
A, 65%; B,12%



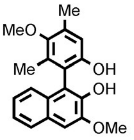
(3): **5c**
A, 76%; B, 48%
A, 70%
(98 mmol scale)



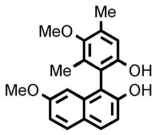
single-crystal X-ray of **5c**
m.p. = 217–218 °C



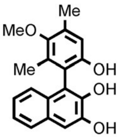
(4): **5d**
A, 75%



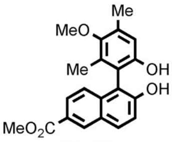
(5): **5e**
B, 70%



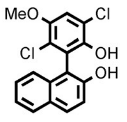
(6): **5f**
A, 60%; B, 55%



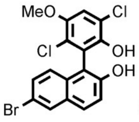
(7):**5g**
A, 70%; B, 60%
A, 68% (1 mmol scale)



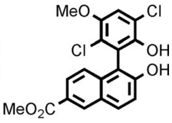
(8): **5h**
A, 90% yield



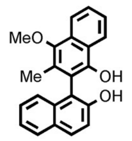
(9): **5i**
A, 15%; B, 68% yield
B, 60% yield (5 mmol)



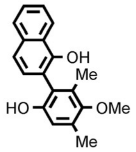
(10)**: 5j**,
A, 72%; A, 60%
(40 mmol scale)



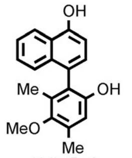
(11): **5k**
A, 64%



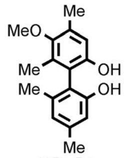
(12): **5l**
A, 70%



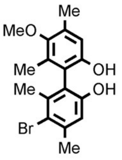
(13): **5m**
A, 69%



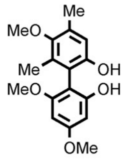
(14)**: 5m'**
B, 80%



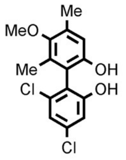
(15): **5n**
A, 54%



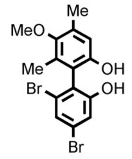
(16): **5o**
A, 65%



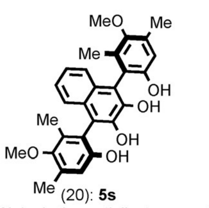
(17): **5p**
A, 65%



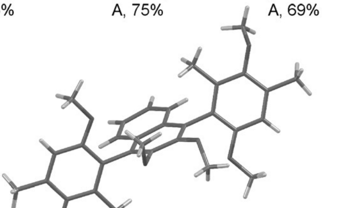
(18): **5q**
A, 75%



(19): **5r**
A, 69%



(20): **5s**
A, 54% (only the *anti* diastereomer)
A, 50% (8 mmol scale)



single-crystal X-ray
of exhaustively O-methylated **5s**
m.p. = 232–235 °C

[a] Reactions were performed on 0.2 or 0.3 mmol scale (0.1 M solution). [b] Yield is that of the product isolated after column chromatography. [c] See the Supporting Information for details on X-ray crystallography.[21]

product biaryldiols ranged between good to excellent. Only in the case of the products **5a**, **5e** and **5i** (entries 1, 5 and 9) were reaction conditions B superior. To our delight, several of these reactions could be readily scaled up. The biaryldiol **5c** was prepared on a 26 gram scale (starting from 98 mmols of **1a**), and it is particularly well-suited for ligand/catalyst synthesis. The structure of **5c** was confirmed using single-crystal X-ray crystallography.[21]

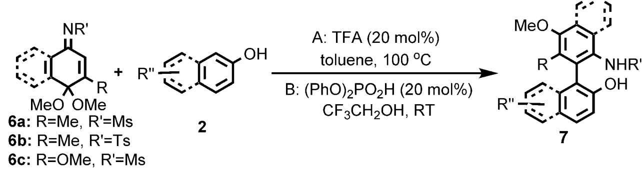
Varying the structure of the quinone monoacetal coupling partner (Table 2, entries 9–12) did not cause any issues, and remarkably an electron-poor 2-naphthol could be coupled with an electron-poor quinone monoacetal to afford the functionalized biaryldiol **5j** (entry 10). The presence of the Br substituent at the 6-position allows further elaboration of the naphthalene nucleus (e.g., by TM-catalyzed cross-coupling reactions). When 1-naphthol was used in the transformation (entries 13 and 14), we were able to control the regioselectivity of the direct arylation reaction (i.e., 2- versus 4-position) by switching between reaction 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, thus allowing the preparation of biaryldiols which have hindered rotation about their chiral axis (i.e., configurationally stable functionalized biaryls).

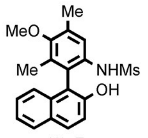
Finally, 2,3-dihydroxynaphthalene can be coupled twice with **1a** to afford the functionalized terphenyl **5s** in good yield upon isolation (Table 2, entry 20). Intriguingly, only the *anti* diastereomer was obtained (i.e., racemic form) while the *syn* diastereomer (i.e., *meso* form) was not observed. This structural assignment was confirmed by subjecting the exhaustively O-methylated derivative of **5s** to single-crystal X-ray diffraction.[21] Nearly all of the biaryldiols shown in

Table 2 are new compounds/structures, previously not accessible in an operationally simple and scalable process.

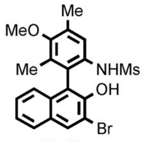
Next, we prepared three iminoquinone monoacetals (**6a**–**c**) and were able to successfully couple these with nine different naphthols (Table 3, entries 1–9 and 12–19) and four different phenols (entries 10, 11, 20, and 21) under the previously optimized reactions conditions A or B. The presence of the sulfonyl group (Ts or Ms) 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]

Table 3: Preparation of non-C_2-symmetrical atropoisomeric 2-amino-2′-hydroxy-1,1′-biaryls (i.e., NOBIN-type) from naphthols and phenols.[a,b]

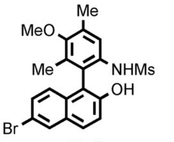




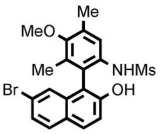
(1): **7a**
A, 84%; B, 92%



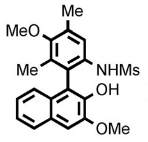
(2): **7b**
A, 84%; B, 60%



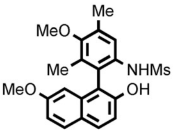
(3): **7c**
A, 89%; B, 64%
A, 87% (2 mmol scale)



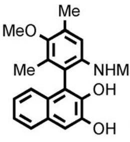
(4): **7d**
A, 90%; B, 57%



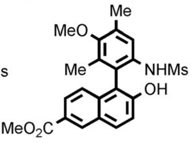
(5): **7e**
A, 71%; B, 84%



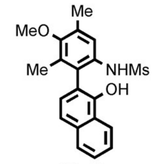
(6): **7f**
A, 94%; B, 58%



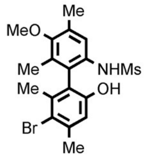
(7): **7g**
A, 58%



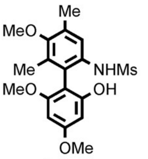
(8): **7h**
A, 82%



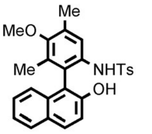
(9): **7i**
A, 76%, B, 59%



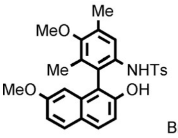
(10): **7j**
A, 47%



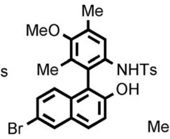
(11): **7k**
A, 80%



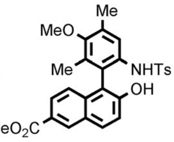
(12): **7l**
A, 85%; B, 82%



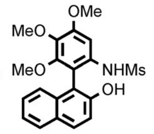
(13): **7m**
A, 87%



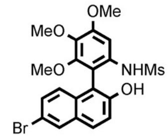
(14): **7n**
A, 88%



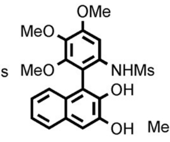
(15): **7o**
A, 94%



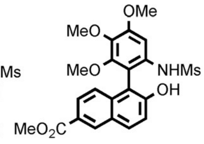
(16): **7p**
A, 64%



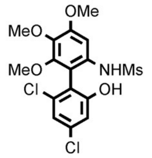
(17): **7q**
A, 74%



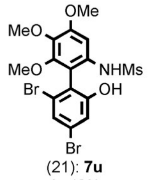
(18): **7r**
A, 67%



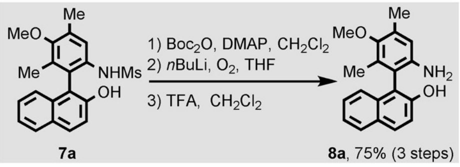
(19): **7s**
A, 66%



(20): **7t**
A, 52%



(21): **7u**
A, 48%



[a] Reactions were performed on 0.2 or 0.3 mmol scale (0.1 M solution). [b] Yield is that of product isolated after column chromatography. Boc = *tert*-butoxycarbonyl, DMAP = 4-*N*,*N*-dimethylaminopyridine, Ms = methanesulfonyl, THF = tetahydrofuran.

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 yields of **5a** (24–72%), the level of enantioinduction was very poor (3–10% *ee*; see details in the Supporting Information). Studies are currently ongoing to develop a catalytic enantioselective version of this coupling reaction.

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 the Supporting Information 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 ($\Delta H^{\neq} < 10\ \text{kcal mol}^{-1}$).[20] Subsequent rearomatization 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).

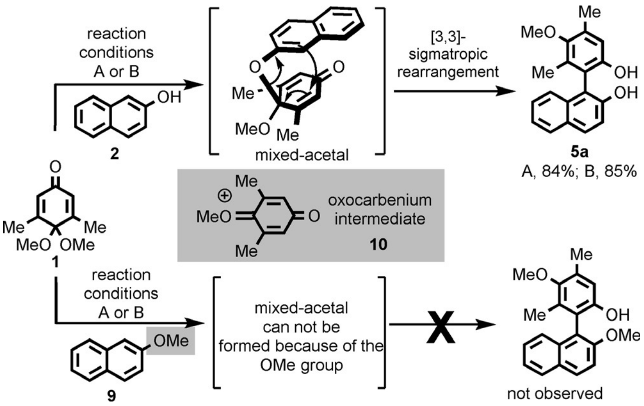


Figure 3. Formation of a mixed-acetal intermediate is not possible with 2-methoxynaphthalene (**9**), thus coupling with **1** does not occur. Unprotected naphthol (**2**) undergoes smooth arylation to afford biaryldiol (**5a**).

We also briefly examined a limited number of alternative reaction pathways. For example, we tested the possibility that 2-naphthol nucleophilicly captures the oxocarbenium intermediate (**10**; Figure 3) which is required for acetal group exchange. This pathway was found to have a barrier which 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 searching for transition states failed to locate a concerted S_N2' transition state.

While nearly all biarly 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 the biaryl **5m′** (entry 14, Table 2) cannot. Rather, **5m′** could be formed by either a [3,5]-sigmatropic shift or an S_N2'-type mechanism (see the Supporting Information for details). Gratifyingly we only observed monoarylated 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 atropoisomeric 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 which build molecular complexity rapidly, with exceptional step-economy and in an environmentally friendly fashion.

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Keywords: atropisomerism · biaryls · organocatalysis · rearrangements · synthetic methods

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[13] A great advantage of this approach is that in the case of the BINOL-type products the OH substituents in the 2- and 2′-positions are directly obtained in their unprotected form and no extra deprotection step is needed. If the biaryl product contains more than one protected OH group (i.e., OMe), selective deprotection of these groups becomes very challenging. Therefore it is desirable to have only the 2- and 2′-hydroxy groups in their unprotected form as it allows the most flexibility with

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[21] CCDC 1436770 (**5c**) and 1436773 (**5s**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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