

Transition-Metal-Free Direct Arylation: Synthesis of Halogenated 2-Amino-2'-hydroxy-1,1'-biaryls and Mechanism by DFT Calculations

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Supporting Information

ABSTRACT: A transition-metal-free, regioselective direct aryl–aryl bond-forming process for the synthesis of halogenated 2-amino-2'-hydroxy-1,1'-biaryls that are currently either inaccessible or challenging to prepare using conventional methods is disclosed. The addition of ArMgX to an *o*-halonitrobenzene at low temperature generates a transient *N,O*-biarylhydroxylamine that rapidly undergoes either [3,3]- or [5,5]-sigmatropic rearrangement in one pot to form a 2-amino-2'-hydroxy-1,1'-biaryl or 1-amino-1'-hydroxy-4,4'-biaryl, respectively. The periselectivity is controlled by the choice of solvent and temperature. This direct arylation process is also readily scalable (1–10 mmol). DFT calculations suggest that from the *N,O*-biarylhydroxylamine intermediate there is a low-energy stepwise pathway that involves initial Mg-mediated N–O bond cleavage followed by pathway branching toward either [3,3]- or [5,5]-rearrangement products via C–C bond formation and rearomatization.

The biaryl structural motif appears in a large number of biologically active natural products, pharmaceuticals, agrochemicals, and functional organic materials (Figure 1).¹ Stereoisomerism (i.e., axial chirality) due to hindered rotation about the C–C bond may also arise in biaryl compounds. The rotational barrier depends on the size and number of substituents at the ortho positions flanking the Ar–Ar bond.² Axially chiral nonracemic biaryls (e.g., NOBIN, BINOL, BINAP) are widely

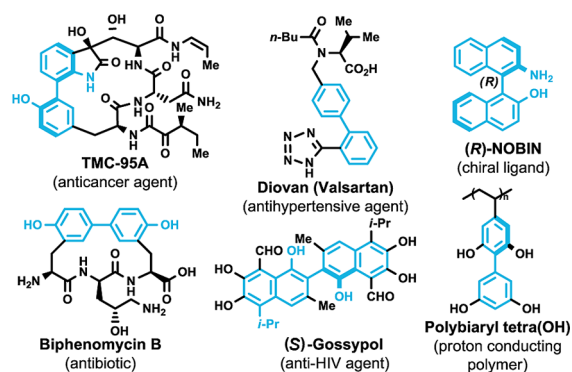


Figure 1. The biaryl structural motif in a range of organic compounds.

used as ligands in a range of catalytic enantioselective processes,³ including several on an industrial scale.^{4,3b} Ar–Ar axial chirality has also been found in more than 1000 natural products, many of which exhibit remarkable biological activities.^{2c} In view of the abundance and importance of the biaryl motif as a privileged structure, a pharmacophore in natural products (e.g., TMC-95A, biphenomycin B, gossypol, etc.; Figure 1) and prescription drugs (e.g., diovan), and a key structural element in ligands for asymmetric catalysis (e.g., NOBIN) and novel organic materials (e.g., liquid crystals, light-emitting diodes, conducting polymers, etc.), it is not surprising that numerous synthetic approaches for its construction have been developed (Figure 2).⁵

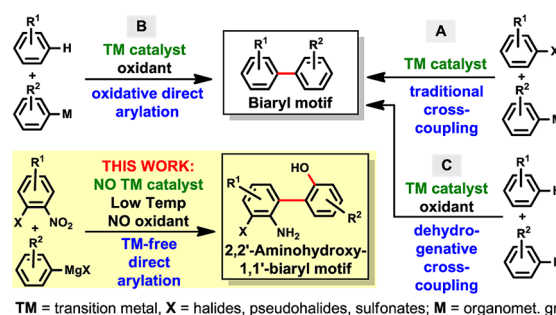


Figure 2. Methods for the intermolecular construction of Ar–Ar bonds, including our novel *transition-metal-free direct arylation* process.

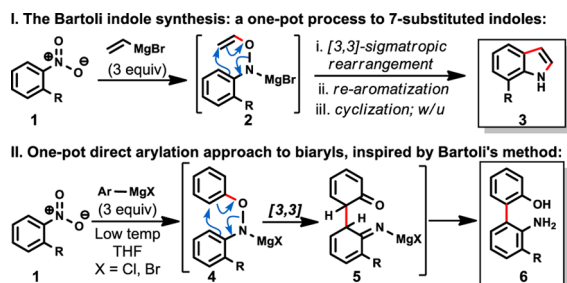
Some of the most widely used Ar–Ar bond-forming strategies include: (1) transition metal (TM)-catalyzed Ar–Ar *traditional cross-coupling*,⁶ which requires prefunctionalization of both coupling partners (e.g., Negishi, Stille, Kumada, and Suzuki reactions, Figure 2A); (2) *oxidative direct arylation*,^{5e,7} which requires prefunctionalization of one coupling partner (Figure 2B); and (3) *dehydrogenative cross-coupling*,⁸ in which neither coupling partner must be prefunctionalized (Figure 2C). Despite the abundance of methods for Ar–Ar bond formation, several biaryl linkages are very difficult to construct in an atom- and step-economical fashion. In particular, 2,2'-diheteroatom-substituted unsymmetrical 1,1'-biaryls (e.g., the highly functionalized 2-amino-2'-hydroxy-1,1'-biaryl motif found in TMC-95A) are not readily accessible and require multiple-step syntheses.⁹

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Our group is pursuing new methods for the synthesis of highly functionalized symmetrical and unsymmetrical biaryls. Ideally, these new routes should (a) be operationally simple; (b) utilize readily available and inexpensive starting materials; (c) avoid the use of TM catalysts, ligands, and strong oxidizing agents; (d) achieve C–C bond formation with high regioselectivity; (e) build molecular complexity rapidly (e.g., in one pot); (f) tolerate functional groups that are generally incompatible with TMs (e.g., halogens, which allow further functionalization via cross-coupling); and (g) complement existing cross-coupling methods by allowing the preparation of currently inaccessible biaryls.

The above attributes present a tall order for reaction design. We were inspired by the intriguing multistep mechanism¹⁰ of the Bartoli indole synthesis¹¹ (Scheme 1), in which intermediate 2,

Scheme 1. Proposed TM-Free Direct Arylation Inspired by the Bartoli Indole Synthesis



presumably formed from the corresponding nitrosoarene intermediate via O-vinylation, undergoes a facile [3,3]-sigmatropic rearrangement to alkylate the aromatic ring at low temperature. We surmised that a similar approach using ArMgX would initially give N,O -biarylhydroxylamines 4,¹² which would furnish highly functionalized 2-amino-2'-hydroxy-1,1'-biaryl products 6 via [3,3]-sigmatropic rearrangement and rearomatization. This reaction would thus result in TM-free direct arylation of unactivated C–H bonds to form a new Ar–Ar bond.

Our choice of 2-bromonitrobenzene (7a) as the first substrate proved to be highly successful. A solution of 7a in tetrahydrofuran (THF) was treated with 3 equiv of PhMgBr (8a) at -78°C and then warmed to 0°C over a period of 30 min. Thin-layer chromatography showed the complete consumption of 7a and the formation of a major polar product identified as 3-bromo-2-amino-2'-hydroxy-1,1'-biphenyl (9a) (see the single-crystal X-ray structure in Table 2). A thorough analysis of the crude reaction mixture revealed the presence of four different products (9a–12), three of which had the same molecular weight based on LC/MS analysis. We presumed that carbazole 10 was formed from a doubly dearomatized intermediate similar to 5.¹³ Formation of the 4,4'-linked biaryl product 11 may be explained by invoking a [5,5]-sigmatropic rearrangement (i.e., similar to the benzidine rearrangement¹⁴) or two sequential [3,3]-rearrangements. N,N -Diarylhydroxylamine 12 could be formed by the direct attack of 8a on the N atom of the in situ-formed nitrosoarene derivative of 7a. The use of solvents other than THF, such as Et_2O , 1,4-dioxane, dimethoxyethane (DME), and toluene led to lower yields of 9a and increased yields of 10 and 12 (Table 1, entries 6–9). A temperature screen in THF (entries 1–5) revealed that the highest isolated yield of 9a was achieved at 0°C (entry 5). Surprisingly, the ratio of the [3,3]- and [5,5]-rearrangement products strongly depended on the temperature. For example, a nearly 1:1 mixture of 9a and 11 formed at -25°C

Table 1. Optimization Studies

Entry ^{a,b}	Solvent	T (°C)	Time (min)	SM (%) (recov.)	Yield (%) ^c			
					9a	10	11	12
1	THF	-78	60	65	0	0	12	0
2	THF	-45	20	37	0	0	20	0
3	THF	-25	20	0	33	trace	29	12
4	THF	-15	20	0	42	8	17	10
5	THF	0	15	0	68	9	0	10
6	Et_2O	0	15	0	58	10	5	12
7	dioxane	10	15	0	46	13	0	16
8	DME	0	60	0	12	15	0	19
9	toluene	0	15	0	50	18	0	10

^a1 mmol scale (0.2 M solution) in the indicated solvent at the indicated temperature and reaction time. ^bUse of PhLi instead of 8a led to complex mixtures. ^cIsolated yields.

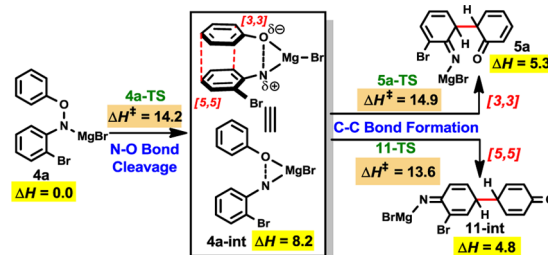
(entry 3), while at 0°C only 9a was detected as the major product (entry 5).

The above results are especially remarkable when compared with the synthesis of N,N -diarylaminines from nitroarenes with functionalized arylmagnesium compounds as reported by Sapountzis and Knochel,¹⁵ where addition of the aryl group at the N atom (i.e., N-arylation) of the nitrosoarene intermediate formed in situ by the reduction of the nitroarene always occurs. In sharp contrast, here the *o*-halonitrosoarene intermediates likely undergo O-arylation to give 4. Clearly, the *o*-halogen substituent changes the regioselectivity of the aryl addition across the $\text{N}=\text{O}$ bond, leading to 1,1'-linked biaryl products that were not observed by Sapountzis and Knochel.¹⁶ Indeed, when exposed to our optimized reaction conditions, *o*-alkyl- and *o*-alkoxy-substituted nitroarenes did not afford even trace amounts of the corresponding 2-amino-2'-hydroxy-1,1'-biaryls.¹⁷

To explore possible reaction mechanisms leading to the [3,3]- and [5,5]-rearrangement products, we performed density functional theory (DFT) calculations at the M06-2X/6-31G-(d,p) level using Gaussian 09.¹⁸ The optimizations shown here were carried out in THF using the SMD¹⁹ solvent model²⁰ [data for toluene and Et_2O are given in the Supporting Information (SI)]. Enthalpies are reported at 0 K.

Scheme 2 outlines the lowest-energy pathways for N–O bond cleavage and C–C bond formation for intermediate 4a. All begin

Scheme 2. Lowest-Energy Pathways for N–O Cleavage and C–C Bond Formation (Energies in kcal/mol)



with MgBr -mediated N–O bond cleavage via transition state 4a-TS ($\Delta H^\ddagger = 14.2$ kcal/mol; Figure 3) to give closed-shell intermediate 4a-int ($\Delta H = 8.2$ kcal/mol). In 4a-TS, MgBr develops chelation with O as the N–O bond stretches from 1.41 Å in 4a to 1.99 Å in 4a-TS. The chelation orients the arene groups in a π -stacked geometry. All attempts to locate a TS for

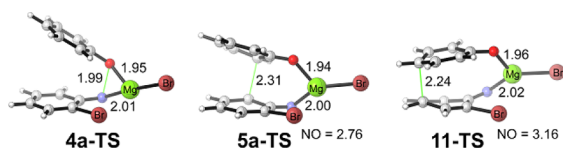


Figure 3. Transition states in the [3,3]- and [5,5]-rearrangements.

concerted [3,3]-rearrangement mediated by MgBr converged to **4a-TS**. From **4a-int** there are several pathways that branch to give C–C bond formation. **5a-TS** ($\Delta H^\ddagger = 14.9$ kcal/mol) is the lowest-energy TS that gives **5a**, which upon deprotonation/rearomatization affords **9a**. The TS for C–C bond formation at the Br-substituted arene C atom is 4 kcal/mol higher in energy than **5a-TS**. The [5,5]-rearrangement product can be accessed through **11-TS**, for which ΔH^\ddagger is 13.6 kcal/mol.

The 0 K enthalpic barriers of **5a-TS** and **11-TS** suggest that the C–C bond formed via the [5,5]-rearrangement is kinetically favored at low temperatures. The ΔG_{298K}^\ddagger values of these TSs are both 15.4 kcal/mol, in qualitative accordance with the increase in **9a** relative to **11** at higher temperatures (Table 1). Modeling of a single explicit THF solvent molecule coordinated to the Mg center did not change the [3,3] versus [5,5] selectivity at 0 K but did show a 0.5 kcal/mol preference for the [3,3]-rearrangement pathway on the free energy surface at 298 K (see the SI).

Intermediates **5a** and **11-int** are endothermic by 5.3 and 4.8 kcal/mol, respectively, raising the possibility that C–C bond formation may be reversible if deprotonation is slow. The TS for intermolecular deprotonation of **5a** by PhMgBr has a barrier of ~ 10 kcal/mol. Intramolecular 1,3- and 1,4-proton transfers have much larger barriers. The 10 kcal/mol barrier for intermolecular deprotonation is close to the barrier for conversion of **5a** back to **4a**, so no definitive conclusion about the reversibility of C–C bond formation can be drawn; however, the correlation between the computed and observed selectivities suggests irreversibility.

With these exciting first results in hand, we examined the scope of nitroarene substrates for this direct arylation process (Table 2). Several *o*-chloro- and *o*-bromonitrobenzenes gave the corresponding 2-amino-2'-hydroxy-1,1'-biaryls in moderate to good isolated yields.²¹ The structure of the nitrobenzene substrate can vary widely, and even multiple halogen substituents are well-tolerated. Likewise, the aryl-Grignard coupling partner can be either monocyclic or fused. In the case of 2-naphthyl-Grignard coupling partners (**8c** and **8d**), the arylation is also regioselective since only the 1-position of the naphthalene ring undergoes arylation (entries 12–25). In none of the reactions could 3-arylnaphthalene products be isolated. There are three general situations in which the yield of the biaryl product tends to be moderate: (a) when the nitroarene contains electron-donating groups (e.g., Me or OMe; entries 3, 7, 17, and 18); (b) when both coupling partners contain electron-donating groups (entry 10); and (c) when the biaryl product is sterically congested and shows atropisomerism (entries 3 and 10). However, steric factors do not seem to have a negative influence on the efficient formation of 1-arylnaphthalene derivatives (entries 19 and 20).

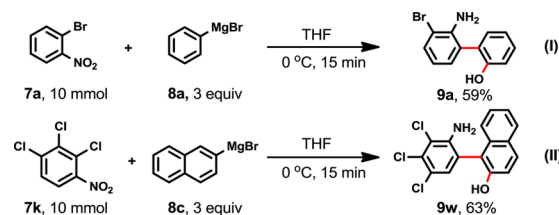
To demonstrate the synthetic utility of this direct arylation process on a multigram scale, we chose two nitroarenes (**7a** and **7k**; Scheme 3) and two aryl-Grignard reagents (**8a** and **8c**) as substrates. To our delight, we found that in just 15 min at 0 °C in THF, biaryls **9a** and **9w** were readily formed in isolated yields of 59 and 63%, respectively.

Table 2. Scope of Substrates and 1,1-Linked Biaryl Products and Single-Crystal X-ray Structures of **9a** and **9n**

Structure of Biaryl Product (Entry) ^{a,b} : Compound #, Isolated Yield (%) ^c			
(1): 9a , 68%	(2): 9b , 51%	(3): 9c , 47%	(4): 9d , 63%
(5): 9e , 48%	(6): 9f , 40%	(7): 9g , 38%	(8): 9h , 64%
(9): 9i , 36%	(10): 9j , 33%	(11): 9k , 62%	(12): 9l , 55%
(13): 9m , 40%	(14): 9n , 49%	(15): 9o , 51%	(16): 9p , 50%
(17): 9q , 31%	(18): 9r , 43%	(19): 9s , 56%	(20): 9t , 55%
(21): 9u , 58%	(22): 9v , 45%	(23): 9w , 67%	(24): 9x , 45%
(25): 9y , 48%			
	9a (m.p. = 161–163 °C)	9n (m.p. = 143–145 °C)	

^a0.2 M solution. ^bThe use of a sacrificial equivalent of Grignard reagent to affect the initial in situ Ar–NO₂ to Ar–N=O reduction led to complex reaction mixtures because of the higher reactivity of nitrosoarenes vs the nitroarene substrates. ^cR_f values and eluents for the products are given in the SI. Side products (e.g., carbazole, hydroxylamine) were readily separated from the products.

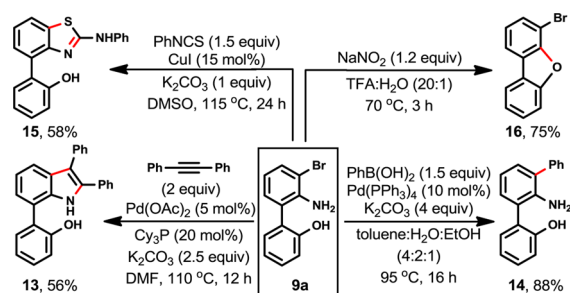
Scheme 3. Direct Arylation on a Multigram Scale



By virtue of their 3-halogen substituents, the 2-amino-2'-hydroxy-1,1'-biaryl products are useful intermediates en route to various unusually substituted heterocycles²² such as indole **13**, benzothiazole **15**, and dibenzofuran **16** (Scheme 4). In addition, Suzuki cross-coupling of **9a** with phenylboronic acid efficiently formed aminohydroxyterphenyl **14**.

In summary, we have developed a regioselective, TM-free, scalable direct arylation method for the synthesis of halogen-substituted 2-amino-2'-hydroxy-1,1'-biaryls. Four distinct processes take place at low temperature in one pot: (i) reduction of the NO₂ group; (ii) O-arylation of the nitrosoarene

Scheme 4. Convenient Preparation of Unusually-Substituted Heterocycles and Terphenyls



intermediate; (iii) [3,3]-rearrangement of the in situ-generated transient *N,O*-biarylhydroxylamine; and (iv) rearomatization. The efficiency of each step is 75–90%. DFT calculations showed that from the *N,O*-biarylhydroxylamine intermediate there is a low-energy stepwise pathway to form the new Ar–Ar bond. The step efficiency and operational simplicity of this transformation allow the rapid generation of molecular complexity and furnish compounds with 1,1'-biaryl linkages that are either very difficult to prepare using conventional methods or otherwise synthetically inaccessible. The resulting structurally diverse halogen-substituted 2-amino-2'-hydroxy-1,1'-biaryl products and their unique heterocyclic derivatives are expected to find broad utility in asymmetric catalysis, drug discovery, and materials science.

■ ASSOCIATED CONTENT

Supporting Information

Experimental and computational details, characterization data, crystallographic data (CIF), and complete ref 18a. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (13) **9a** could not be converted to **10** under strongly basic conditions (i.e., excess **8a**). Thus, it is reasonable to assume that once **9a** is formed, it does not convert to **10** under the reaction conditions.

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