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C–C Coupling |*Hot Paper*|

Formaldehyde-Extruding Homolytic Aromatic Substitution via C⟶O Transposition: Selective 'Traceless-Linker' access to Congested Biaryl Bonds

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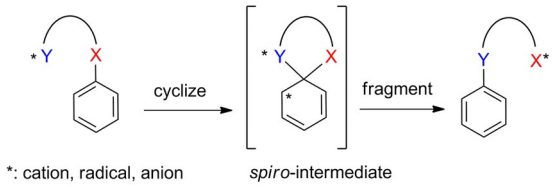
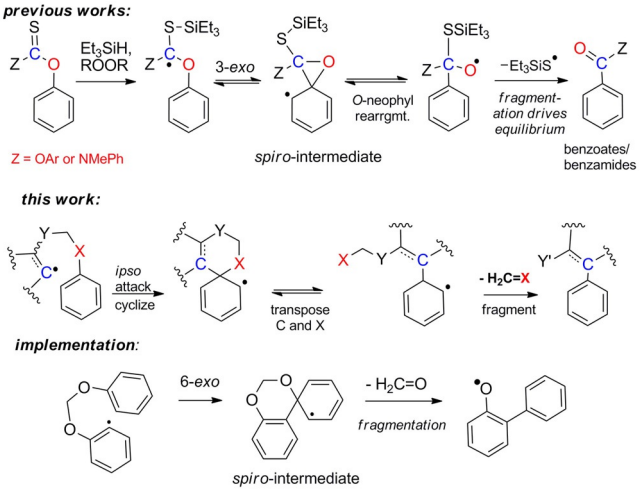
Abstract: A new, selective way to form C–C bonds has been developed. In this report, we disclose the homolytic aromatic substitution via C⟶O transposition coupled with the elimination of formaldehyde (as a traceless linker). Computational analysis indicates the selectivity can be tuned by sterics in the starting materials following an *ipso*-attack that leads to the C⟶O transposition.

New methods for the selective formation of C–C bonds continue to be important in organic chemistry. A useful approach for a metal-free selective creation of this key organic structural unit involves use of X⟶C transpositions. In these processes, the initially present C–X bonds serve as an anchor and a directing tool for the creation of a new C–C bond at the same position. In a later stage of the process, the initial C–X bond is broken in a fragmentation step (Y = C, Scheme 1).

Synthetic utility of such processes is illustrated by a radical O⟶C transposition that transforms phenols into benzoic acid derivatives via intermediate thiocarbonates or thiocarbamates.[1] The transposition cascade proceeds via cyclization at the aromatic π-system leading to a bicyclic spiro-intermediate. If this cyclization makes a three-membered ring, the subsequent C–O bond scission leaves atom X (the only atom of the "tether") at the carbon of the new C–C bond (Scheme 2). If a weak C–Z bond is present at the same carbon, this cascade is terminated by a C–Z fragmentation step yielding a carbonyl compound (X = O).



Scheme 1. General concept for intramolecular X⟶Y transposition at an aromatic ring. X is a directing group that enables cyclization of reactive functionality, Y*, at the *ipso*-position (i.e., *exo*-cyclization) with the formation of bicyclic spiro-intermediate, fragmenting to the transposed product.



Scheme 2. The earlier examples of radical O⟶C transpositions coupled with fragmentations via a transient three-membered ring and the current design with a transient six-membered ring.

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The present work is driven by a new hypothesis: if an *n-exo*-transposition process with a tether $n>3$ is used, the atom X is moved further away from the point of attachment after the spiro-intermediate is opened. In the ideal scenario, the X-bearing directing group is eliminated from the product in a subsequent step, revealing a previously hidden functionality.[2] In this work, we will show how this concept applies for the preparation of sterically hindered biaryls.

The biaryl bond is prominent in natural products and pharmaceuticals. Sterically hindered 2-hydroxy-biaryl natural products include secalonic acid D[3] (**2**, Figure 1), 6-hydroxyjusticidin A (**3**), and ancistrotectoriline C (**4**), and manufactured pharmaceuticals include the antibiotic vancomycin (**1**).[4] Furthermore, biaryl ligands, such as phosphines based on **5** (e.g. SPhos, $R^1=Me$, $R^2=OMe$, $R^3=Cy$;[5] $R^1/R^2=H$, $R^3=Cy$), are important for transition-metal catalysis. Biaryl phosphine ligands based on **5** (e.g. SPhos, $R^1=Me$, $R^2=OMe$, $R^3=Cy$;[5] $R^1/R^2=H$, $R^3=Cy$).[6]

A novel application for transposition is in the synthesis of particularly challenging sterically hindered biaryl bonds, of the types seen in the prominent natural products and ligands of Figure 1. Since 1901,[7] such targets have been more popularly attained with transition-metal-mediated reactions. In this context, cross-coupling and, more recently, C–H functionalization, have often dominated the popular designs.[8] Our arylation makes use of the homolytic aromatic substitution (BHAS).[9]

This radical approach commonly involves reaction at one of the three following positions: a) position substituted with the appropriate leaving group, b) unsubstituted CH moiety, c) or carbon that is *ortho*- to the position of an intramolecular tether. It is quite rare[10–12] to see the biaryl bond formed at the neighboring *ipso*-position (see Scheme 2). Some sterically hindered biphenyls remain nonetheless difficult to access via any/all of these routes,[13] and (differentially) tetra-*ortho*-substituted biaryls are known to be often challenging targets.[14] Discovery of reliable and high-yielding reactions for their synthesis is considered a valuable goal.[15]

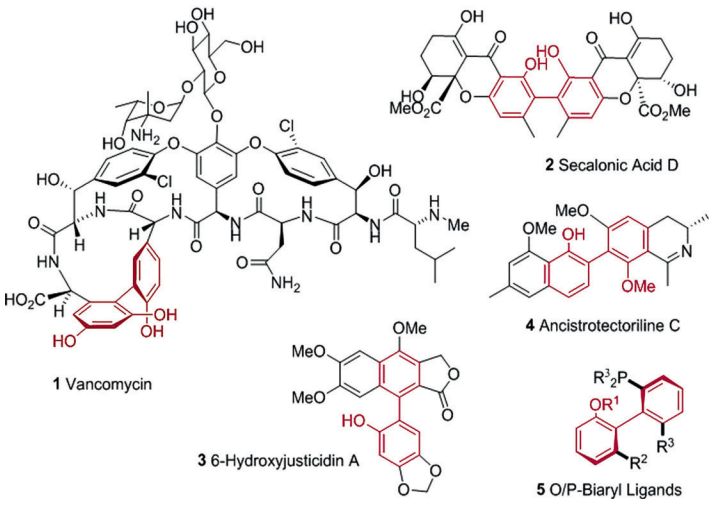


Figure 1. Sterically-hindered (2-oxy)biaryl targets prominent as natural products and ligands.

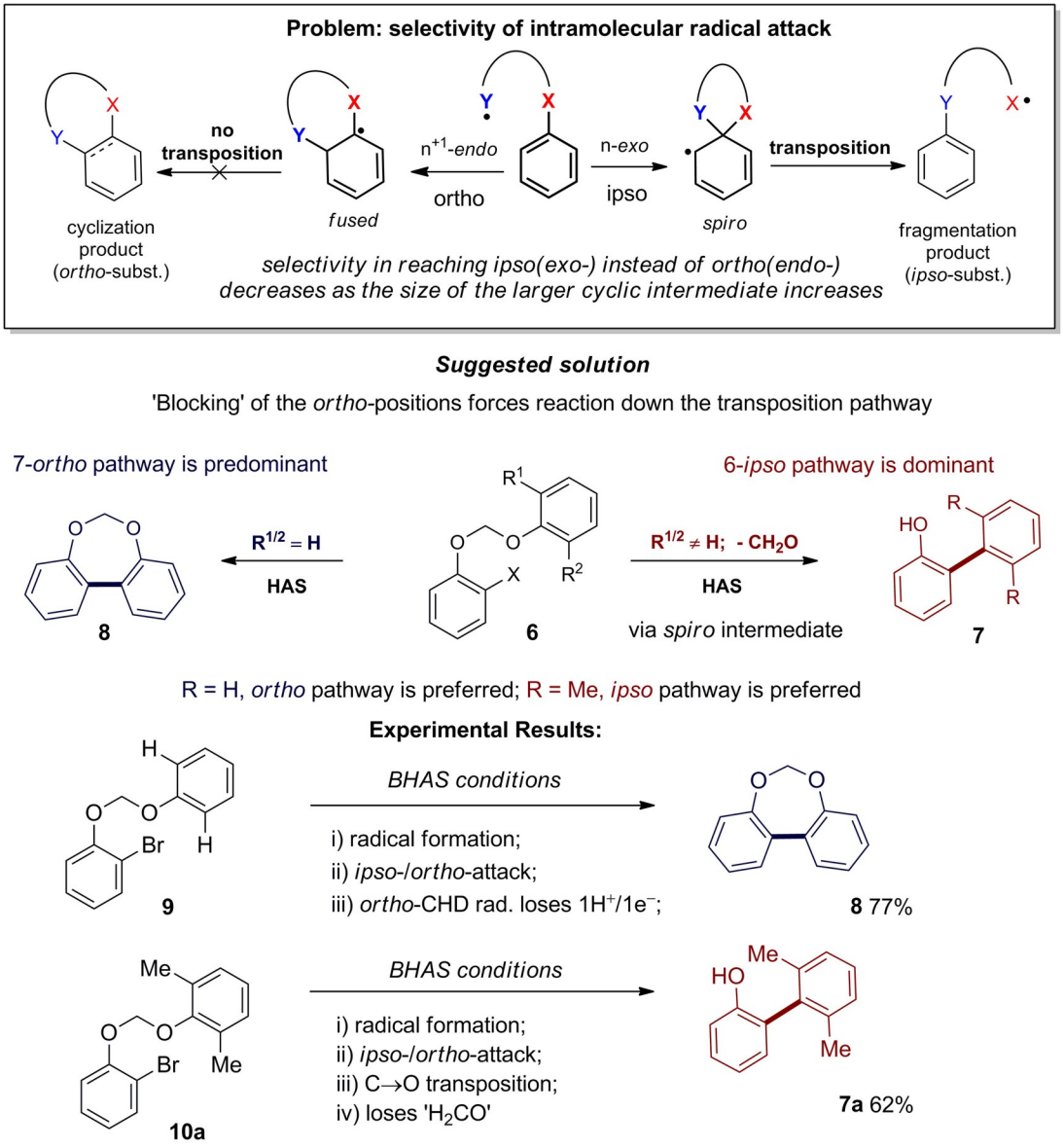
The key problem for designing new transposition strategies is that they rely on *exo*-selectivity (i.e. the formation of spiro rather fused intermediates, see Scheme 3).[16] Unfortunately, this selectivity, perfect in the 4-*ortho*/3-*ipso* pair, erodes for the larger cycles (e.g., 7-*ortho* vs. 6-*ipso*). We report herein one experimental solution to this problem, based on the enhanced selectivity of attack at the *ipso*-position with a disubstituted (i.e. 2,6-dimethylated) ring, a steric imposition at the *ortho*-positions. The advantage of this strategy is that it also provides an attractive synthetic route to sterically hindered biphenyls, an important group of synthetic targets. Experimental findings are complemented with computational analysis that reveals the origin of dramatic change in selectivity imposed by the *ortho*-substitution; showing how the individual pieces of the O→C transposition cascade puzzle gather into an efficient transformation.

Computational analysis: methodology

All calculations were carried with the Gaussian 09 software package,[14a] using UM06-2X DFT functional[17,18] or the MP2 method,[19] both with the 6–311++G(d,p) basis set, commonly used for the analysis of radical processes. UM06-2X/6–311++G(d,p)/aug-cc-pV5Z-PP+ECP method was used to calculate the redox properties of PhI. The latter method was used solely for analyzing four different conformations of the starting material. Delocalizing interactions were evaluated with natural bond orbital (NBO) method, using NBO 3.0 software. NBO analysis transforms the canonical delocalized molecular orbitals from DFT calculations into localized orbitals that are closely tied to the chemical bonding concepts. Each of the localized NBO sets is complete and orthonormal. The filled NBOs describe the hypothetical, strictly localized Lewis structure. The interactions between filled and antibonding orbitals represent the deviation from the Lewis structure and can be used to measure delocalization. For example, delocalizing interaction can be treated via the 2nd order perturbation energy approach $E(2)=n_i|F_{ij}|^2/\Delta E$, where n_i is the population of a donor orbitals, F_{ij} is the Fock matrix element for the interacting orbitals i and j, and ΔE is the energy gap between these orbitals. Chemcraft[16a] and CYLView[16b] were used to render the orbitals and molecules.

Ph-substituted substrates

Potential energy surface (PES) for the parent system (Scheme 4) provides the needed quantitative comparison of the two possible cyclization pathways (spiro vs. fused). In the absence of steric constraints, the phenyl radical prefers to attack the *ortho*-carbon instead of the *ipso*-carbon of the second phenyl ring. The *ortho*-attack barrier is a 4.9 kcal mol^{-1} lower and the 7-membered radical resulting from the *ortho*-attack can be stabilized by a *2c,3e* interaction with the lone pairs of the oxygen substituent.[20] Both cyclizations are strongly exergonic and should be irreversible.



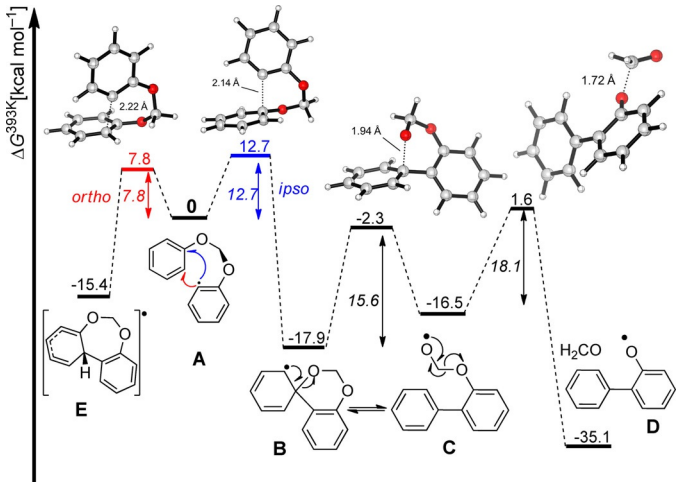
Scheme 3. Top: Transposition biarylation and the regioselectivity issue. Bottom: Switch in the dominant reaction pathway is observed upon changing of the *ortho*-R groups (here, H→Me).

Although the *ipso* pathway is not accessible in the parent system, the further steps along this option were explored computationally to provide the benchmark data for the energetics of C→O transposition. The spiro radical B can undergo a C–O scission into an isomeric O-centered radical C. The process is relatively fast due to the stereoelectronically favorable alignment of the breaking C–O bond and the radical center,[2,21] and further facilitated by rearomatization. However, due to the dramatic loss of radical delocalization, this step is slightly endergonic (by 1.4 kcal mol^{-1}) and would be reversible if our reaction design had not incorporated the other, now highly exergonic, C–O scission. This last step releases formaldehyde and traps the translocated C→O radical in a deep potential energy well.

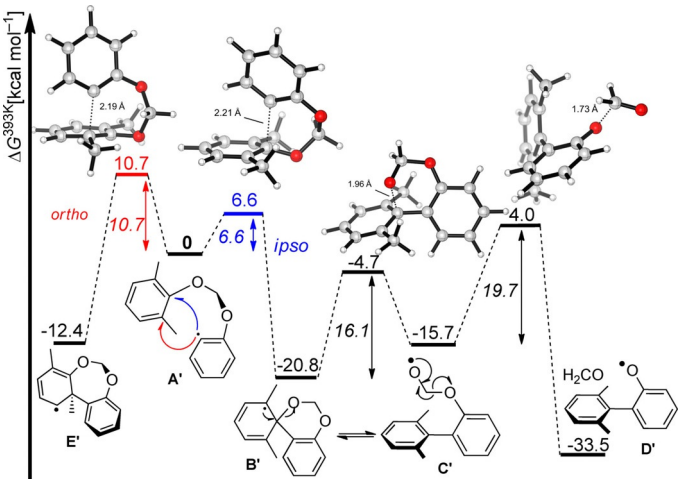
The effect of *ortho*-Me groups

The introduction of methyl groups dramatically reshapes the potential energy surface in favor of the *ipso* attack. The calculated $\Delta\Delta G^{\neq}$ value (4.1 kcal mol^{-1}) suggests $\approx 10^3$ kinetic preference for this path. As expected, part of this reversal of selectivity originated from the steric hindrance imposed by the Me groups on the *ortho*-cyclization (10.7–7.8 = 2.9 kcal mol^{-1}). However, much larger was the accelerating influence of these substituents on the *ipso* cyclization (12.7–6.6 = 6.1 kcal mol^{-1}), suggesting that the methyl groups also impose a stabilizing effect on the TS and product of the spiro cyclization. The rest of the O→C transposition cascade is not perturbed by the substitution (Scheme 5).

The conformational preorganization of starting material towards the reactive conformation was also analyzed



Scheme 4. The calculated PES for R = H favors the *ortho*-attack and prevents the C→O radical transposition cascade originating from the *ipso*-attack.



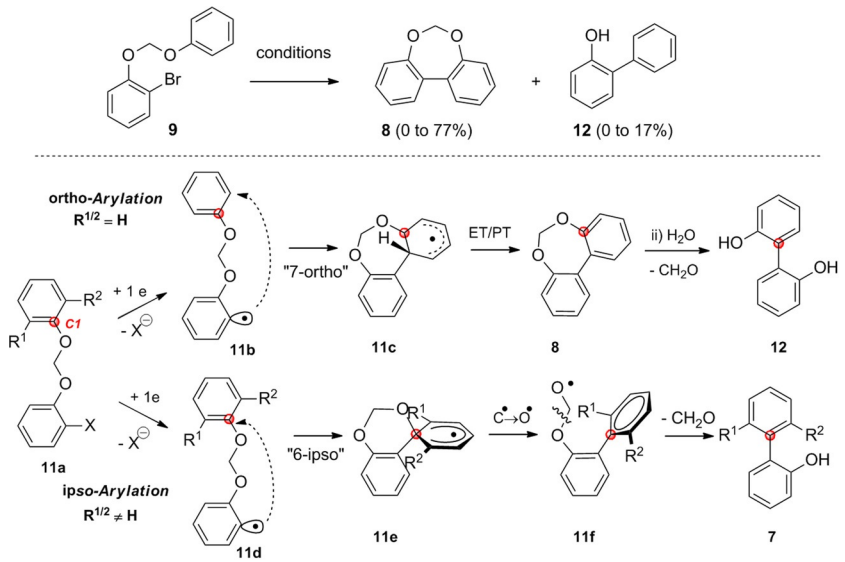
Scheme 5. Calculated PES for R = Me in terms of ΔG (kcal mol^{-1}), following the *ipso*-attack. *Ortho*-attack was also computed for comparison. Final step is favored due to entropic contribution.

(Supporting Information). Comparison of stereoelectronic factors and stabilities indicates the key role of the anomeric effect in pre-organizing this acyclic system towards the reactive "near attack" conformation.[22,23]

Experimental results: background

During optimisation of the "acetal method" part of the investigations of the BHAS reaction[3a,b,9a,b]—two of us reported the isolation of 2-phenylphenol (**7**) as a by-product.[3b,24] The procedure employed a molecular tether placed in sequence to form heterodimers with 2-bromophenol resulting in a methylene bridge and the namesake acetal. Under the BHAS conditions (i.e. in the presence of potassium *tert*-butoxide and 1,10-phenanthroline at elevated temperature), the substrate (**9**, Scheme 6) loses bromide to form a sigma-radical (intermediate **11 b/d**, Scheme 6) at the *ortho*- position leading to an intramolecular cyclization of the tethered substrate to a dibenzo-[1,3]-dioxepine, **8**. The tether can be removed in a subsequent step in aqueous acid to furnish the 2,2′-biphenol **12**.

The dibenzo-[1,3]-dioxepine (**8**, Scheme 6) and 2-phenylphenol **7** are products of two cyclization pathways, that is, 7-*ortho* and 6-*ipso*, diverging from a common radical intermediate **11 b/d** generated via the mechanism proposed by Studer and Curran.[25,26] The 7-*ortho* cyclization forms the intermediate **11 c** followed by subsequent formal H abstraction (i.e., the sequence of deprotonation and electron transfer in the BHAS mechanism) to produce the dibenzo-[1,3]-dioxepine **8**. The 6-*ipso* cyclization to **11 e** invokes an intriguing mechanistic pathway, whereby a radical rearrangement described as a C→O transposition and fragmentation excises a CH_2O unit from the molecule. It should be noted that *ortho*-hydroxy(aryl)arenes can be synthetically challenging—traditional methods of biaryl coupling offer poor reactivity for the position *ortho*- to the phenol. Not only are these positions traditionally considered

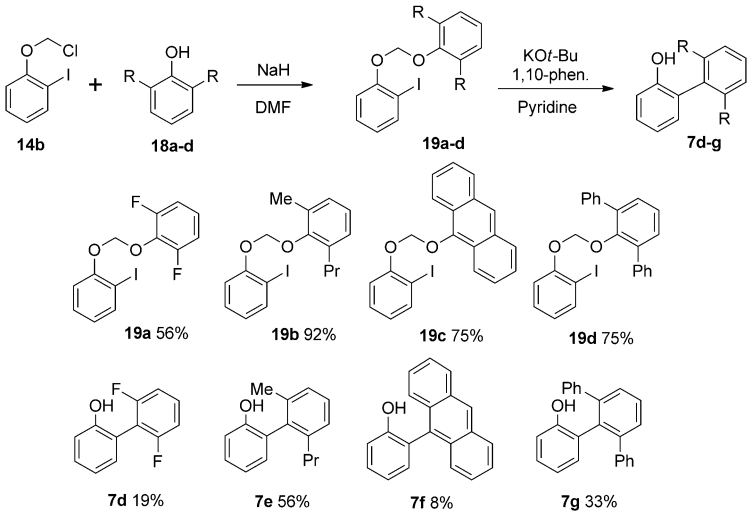


Scheme 6. Top: Initial report of the C→O transposition. Heating via microwave irradiation (MWI). Aromatic solvent, KO*t*Bu (1.0–3.0 equiv), 1,10-phen. (40 mol%), 80–120 °C.[3] Bottom: Regio-outcomes and mechanisms of the *ortho*- vs. *ipso*- arylation.[25].

deactivated to Pd^0 insertion, they are also not compatible with the application of organometallics due to phenolic OH acidity.

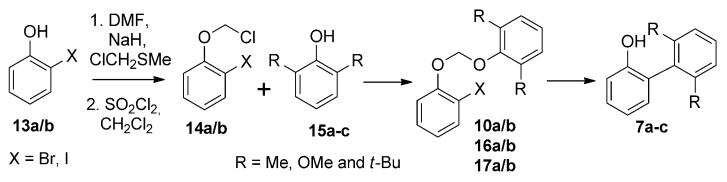
Synthesis of *ortho*-arylated phenols using the "acetal method" required promotion of the minor 6-*ipso*-cyclization over the normally favoured 7-*ortho*-cyclization. Hence, acceptor arenes were assembled with *ortho*,*ortho*-disubstituted phenols. The yields of subsequent polysubstituted biaryls products traditionally suffer with increasing steric clash due to substitution around the biaryl bond. In our design, the same factor drives the transformation.

A comparative study was conducted between acetals constructed from the iodo- and bromo- substrates derived from 2,6-dimethyl, 2,6-dimethoxy, and *tert*-butyl phenols (Table 1). The resulting acetals **10a/b**, **16a/b**, **17a/b** underwent C→O transposition, followed by linker extrusion to produce the 2-arylphenol products **7a–c** (Table 1). Iodo-activated BHAS substrates slightly outperformed the Br analogues.



Scheme 7. Synthesis of acetals and C→O radical transposition products derived from 2-iodophenol.

Table 1. Comparison of Ar-Br (**10a**, **16a**, **17a**) and Ar-I (**10b**, **16b**, **17b**) precursors.



Ar′OCH$_2$OAr/2-Ar′ArOH	X	R	Yield [%] (X)Ar′OCH$_2$OAr	Yield [%] 2-Ar′ArOH
10a/7a	Br	Me	76	62
16a/7b	Br	OMe	72	54
17a/7c	Br	*t*-Bu	54	10
10b/7a	I	Me	83	65
16b/7b	I	OMe	82	60
17b/7c	I	*t*-Bu	59	24

Although the difference was small for the di-Me substrates **10**, it became more pronounced in the sterically demanding 2,6-di-*tert*-butyl derivatives **17**.

Using the preferred iodoarene substrates, the scope was broadened to less familiar substrates and non-symmetrical phenols. Acetals were constructed from 1-(chloromethoxy)-2-iodobenzene (**14b**) (Scheme 7) and the respective 2,6-disubstituted phenols (**18a–d**) in good yields (56–92%, 3 steps).[3b] An exception was 9-hydroxyanthracene **18c,** which was generated by deprotonation of anthrone and trapped as the acetal **19c**.

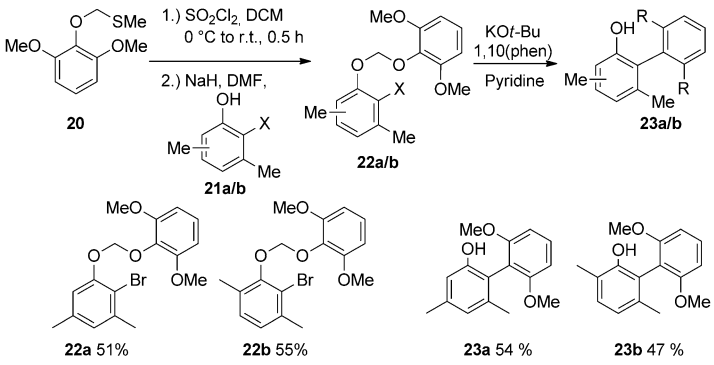
The yields of BHAS reactions were sensitive to the structure of starting materials. In particular, derivatives **7d** and **7f** (Scheme 7) returned de-halogenated/non-cyclized acetals (not shown) along with the unreacted starting material.

We further sought to test the approach in providing access to products fully substituted at all four *ortho*-positions around the biaryl bond. These products were produced by functionalizing an appropriate 'receptor' halophenol with an active tether in the form of the chloroacetal derived in situ from thioacetal **20** (Scheme 8).

This species was substituted with the 2-bromophenols **21a/b**, completing the acetal substrates **22a/b** in satisfactory yields (given the highly substituted nature of the aryloxy nucleophiles). In the subsequent formation of the 2-arylphenols via the new C→O radical transposition, we extended the reaction time from 2 to 4 hours, which resulted in acceptable yields of tetra-*ortho*-substituted biaryls (**23*a*** = 54%, **23*b*** = 47%).[9c]

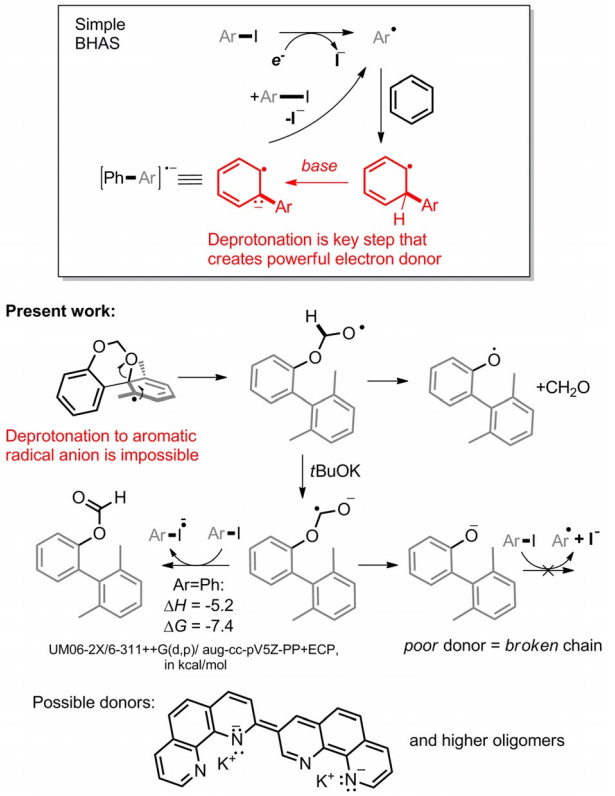
New insights into the nature of donor species in the BHAS mechanism

Importantly, this cascade transformation offers new insights into the mechanism of BHAS processes. In particular, it pro-



Scheme 8. C→O radical transposition synthesis of tetra-*ortho*-substituted biaryls **23a** and **23b.**

vides a way to evaluate the nature of possible electron donors in the catalytic cycle where the "electron is the catalyst".[25] In the usual version of this process, the key electron donor that closes the catalytic cycle is an aromatic radical anion that is formed via deprotonation of a delocalized π-radical by the base (Scheme 9, top). Due to the *ipso*-attack in the



Scheme 9. Comparison of the usual BHAS mechanism where deprotonation of a radical leads to highly reducing aromatic radical anion with the present cascade process where such process is impossible. An intriguing possibility is that the needed reducing power in these cascades is created from organic superdonors formed from the dimerization of phenanthroline ligands.

C–C bond-forming step, there is no proton at the respective position in the delocalized π-radical intermediate of our cascade. Hence, the cascade continues via a radical fragmentation step. Even though one can consider deprotonation of the α-position of the O-radical formed in this step, this step is likely to lead to C–O bond scission into a stable phenoxide anion that is unlikely to propagate the cascade. The calculated free energies in Scheme 9indicate that it is thermodynamically feasible for the ketyl radical anion to serve as a chain-propagating reductant for the conversion of aryl iodides to aryl radicals. However, this only would be possible if the conversion into phenoxide anion is slow. Because the experimental cascade works, we suggest that this experimental observation provides evidence to the important role of organic superdonors that can be formed in situ under these conditions from phenanthroline ligands, as suggested by Murphy, Tuttle, and co-workers.[9e,27] Dimerization of the ligand provides a potential two-electron donor, so 40 mol% of phenanthroline could provide 40 mol% of electrons. Potentially, additional reducing power needed to form aryl radicals from haloarenes could arise from further similar oligomerisation of the dimers by *t*BuOK. The importance of this pathway as well as the possible involvement of formate radical anions needs to be addressed in the future studies.

Conclusion

Intramolecular BHAS reaction of substrates blocked at the 2,6-positions on the receptor ring provides reliable access to synthetically challenging biaryls. This unusual reaction is also interesting from a mechanistic standpoint: the unique C–O transposition in the system is driven by the extrusion of the tether in the fragmentation and loss of formaldehyde. This inexpensive transition-metal-free reaction can find utility in natural product synthesis, in which sterically demanding biaryls are plentiful. Not only that, but it can also serve as a new route to many other classes of highly useful biaryls, such as the Buchwald class of phosphine ligands.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–C coupling · density functional calculations · radicals · reaction mechanisms · spiro compounds

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