HAT Catalysts to Facilitate Acid Mediated Cleavage of Biaryl C-C Bonds in Binaphthols

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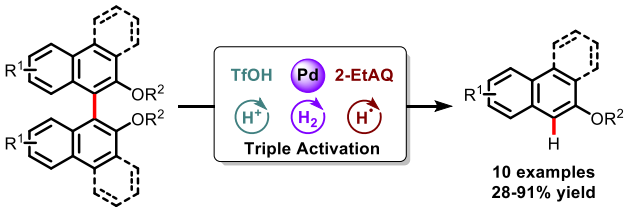
Supporting Information Placeholder

ABSTRACT: A method to cleave the C-C biaryl bond of binaphthyl derivatives under reductive conditions is described. Triflic acid employed together with a catalytic HAT reagent, 2-ethyl-9,10-dihydroxyanthracene that is regenerated using H_2 with catalytic Pd/C, yielded monomeric products in improved yields. A range of substrates is disclosed and kinetic analyses provide insight into the mechanism of aryl–aryl activation.



Activation of carbon–carbon (C–C) bonds has provided unique solutions to adding molecular complexity.[1, 2] Numerous methods of C–C activation have been developed, however, most studies focus on polarized bonds such as C–CN, or C–carbonyl bonds.[3-5] Historically, activation of non–polarized bonds such as aryl–aryl C–C bonds have been challenging and often require strained bonds such as those found in biphenylene.[6, 7] Methods for the activation of unstrained aryl–aryl bonds are desirable for the valorization of lignin. Lignin is a biopolymer found especially in trees and is a major waste product of the paper pulping industry contributing to 10–50 million tons being produced annually with much of it being burned as fuel.[8] The polyphenolic structure of lignin (Figure 1) is made up of many different subunits, one of which is the 5–5' biaryl linkage which makes up to 30% of linkages in some spruce woods.[9] Therefore, strategies to functionalize these linkages found in lignin into higher value added products have great value.

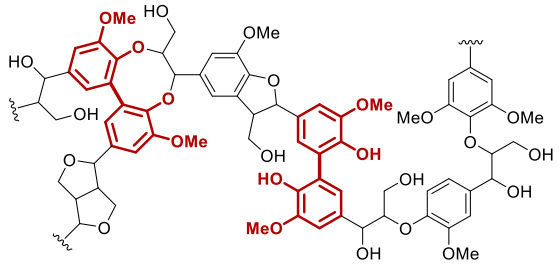
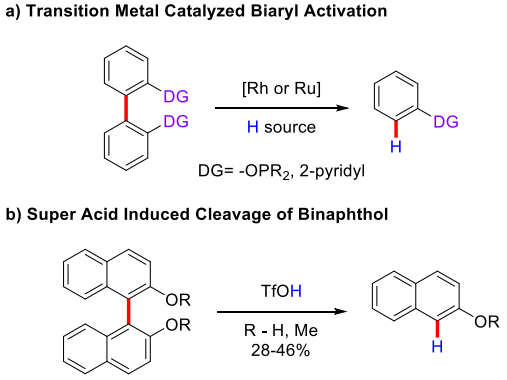


Figure 1. Representative structure of lignin with 5–5' linkages highlighted in red.

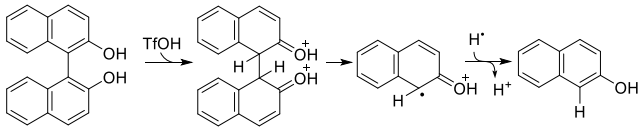
In recent years, elegant methods for activating unstrained aryl–aryl bonds using rhodium and ruthenium have been developed by the Dong and coworkers (Scheme 1a).[10, 11] These systems require specific directing groups such as phosphinite or 2-pyridyl groups in order to activate the C–C bond. Work by Koltunov and coworkers provides an alternative approach that utilizes super-acids such as triflic acid (TfOH) to both racemize and cleave the C–C binaphthyl bond of 1,1'-bi-2-naphthol (BINOL) (Scheme 1b).[12, 13] Obtaining high yields proved challenging (28-50%) and few substrates have been examined. Herein, we report the use of a hydrogen-atom transfer (HAT) catalyst in combination with acid for the cleavage of the aryl-aryl bond in binaphthol derivatives.

Scheme 1. Methods for Aryl–Aryl Activation



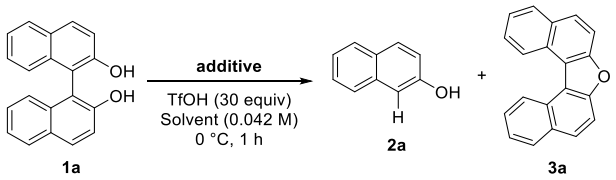
For the reaction in Scheme 1b, a hydrogen atom abstraction is needed after homolytic cleavage of the bisprotonated binaphthol derivative in order to generate the monomeric 2-naphthol derivative as shown in (Scheme 2). It was unclear what the source of this hydrogen atom would be in the transformation with TfOH, the most likely source being the substrate which could lead to other reaction pathways.[13] We hypothesized that a single electron reductant would therefore facilitate the overall transformation.

Scheme 2. BINOL Cleavage with TfOH



Examining the conditions previously reported,[13] the reaction in $CHCl_3$ (Table 1, entry 1) provided 24% of **2a** (vs 28% reported)[13] with a moderate 62% conversion. Other nonpolar solvents (entries 2-5) did not improve the yield of **2a** even though improved conversions were noted in all cases. The higher conversion yet lower yield may be a result of greater reactivity resulting in uncontrolled oligomerization as evidenced by the large amount of insoluble precipitate observed in entries 2-5. An explanation for the difference in reactivity between chloroform and these other solvents may arise from the greater ability of chloroform to stabilize proposed cationic intermediates.[14] Even greater stabilization would be expected from aprotic solvents such as DMF, MeCN, and THF (entries 6-8); however, they provided negligible conversion and no product. These basic solvents are likely exhaustively protonated by triflic acid and the resultant conjugate acids are not sufficiently acidic to allow arene protonation.[15-17]

Table 1. Solvent and Additive Screen



entry	solvent	additive (equiv)	Conv (%)[a]	**2a** (%)[a]	**3a** (%)[a]
1	$CHCl_3$	—	62	24	—
2	PhMe	—	>99	8	—
3	PhCl	—	>99	11	—
4	DCE	—	94	8	—
5	CH_2Cl_2	—	100	12	—
6	DMF	—	14	0	—
7	CH_3CN	—	17	0	—
8	THF	—	0	0	—
9	CH_2Cl_2	ferrocene (2)	82	15	45
10	CH_2Cl_2	ferrocene (5)	89	<1	56
11	CH_2Cl_2	KI (2)	81	15	54
12	CH_2Cl_2	6-MeO-2-Nap (2)	>99	49	12
13	CH_2Cl_2	HQ (2)	100	54	3
14	CH_2Cl_2	AQ (0.2)[b]	100	80[c]	4
15	CH_2Cl_2	2-EtAQ (0.2)[b]	100	83[c]	3

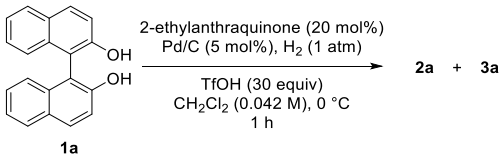
[a]Determined by ^1H NMR spectroscopy using CH_2Br_2 internal standard. [b]Includes Pd/C (5 mol%) and H_2 (1 atm). [c]Isolated yields.

As the yield of the monomer was low in all cases, presumably due to additional decomposition pathways, efforts shifted to screening additives with the most reactive solvent, CH_2Cl_2 (Table 1 entries 9–15). A major obstacle to overcome is the uncontrolled oligomerization resulting from a build up radical–cation created following homolytic cleavage of the C–C bond (Scheme 2).[13] To accelerate the conversion of the radical cation to the product and thereby mitigate these unwanted side-reactions, one-electron reductants were investigated (entries 9–11). However, these additives did not reduce the radical cation intermediate directly to naphthol **2a**. Instead, a new major product was formed, which upon isolation was determined to be the cyclized product **3a**.

Hydrogen atom transfer reagents were next investigated (entries 12–15). Using a sacrificial hydrogen atom donor would prevent the radical cation intermediate from abstracting hydrogens from unreacted starting material or product present. Reasoning that electron-donating groups on a naphthol would stabilize the radical and result in a a better H-atom donor relative to **1a** or **2a**, 6-methoxy-2-naphthol was examined and was found to result in an improved yield of 49% (entry 12). Hydroquinone (HQ, entry 13) led to a further increase in yields at 54%; however, the poor solubility of hydroquinone limited its efficiency. To both improve solubility and reduce the amount of additive needed, 9,10-dihydroxyanthracene, generated in-situ from anthraquinone (AQ) with Pd/C and H_2 gas[18], was used and a substantial increase in yield was observed (entry 14). Use of 2-ethylanthraquinone (2-EtAQ), which shows improved solubility in organic solvents compared to AQ,[19] saw the highest yield at 83% (entry 15).

A series of control reaction was undertaken to delineate the role of each component of this transformation (**Table 2**). Removal of 2-EtAQ or Pd/C resulted in substantially decreased yields (entry 2–3). The decrease in yield observed upon removal of Pd/C suggests that 2-EtAQ directly inhibits the reaction most likely by acting as a base toward TfOH. In the presence of Pd/C

Table 2. Control Reactions



	variation on standard conditions	**2a** (%)[a]	**3a** (%)[a]
1	none	83[b]	3
2	no 2-EtAQ	23	4
3	no Pd/C	10	<1
4	no TfOH	0	0
5	10 mol% 2-EtAQ	78	7
6	2.5 mol% Pd/C	81	9
7	15 equiv TfOH (0.084 M)	60	11
8	5 equiv TfOH for 5 h	24	64
9	30 equiv MsOH	0	4

[a]Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 internal standard [b]Isolated yield.

hydrogenation to 2-ethyl-9,10-dihydroanthracene leads to a species that is less basic and can act as a hydrogen atom donor. A decrease in rate at increased loading of 2-EtAQ further supports this theory (see below). Removal of triflic acid (entry 4) resulted in no conversion. Halving the amount of Pd/C or 2-EtAQ provided comparable yields of **2a**, but did increase the amount of **3a** produced (entries 5-6). Reducing the amount of TfOH resulted in substantial decreases in yield of **2a** and much larger amounts of **3a** (entries 7-8). Finally, use of the less acidic methanesulfonic acid in place of TfOH resulted in no **2a** and small amounts of **3a**.

Several binaphthyl derivatives were investigated using the optimal conditions (**Figure 2**). Methylated BINOL proceeded similarly to BINOL (**2b** vs **2a**). Addition of methyl groups to the C3,C3'-positions was well tolerated (**2c**, 71%), but the same substitution at the C7,C7'-positions resulted in lower yield (**2d**, 60%). The latter favors protonation at the 6- and 8-positions preventing productive protonation of the 1-position.[12] While phenyl substituents at C4,C4' were well-tolerated (**2e**, 79%), introduction of trifluoromethyl or methoxy groups onto the C4,C4'-phenyl resulted in lower yields (**2f**–**2h**). The electron-withdrawing nature of the 4-CF_3 and 3-MeO substitutions (**2f**, **2h**) are consistent with less effective protonation of the binaphthyl system. The lower yield with the more electron-donating 4-MeO analog **2g** is attributed to protonation of the methoxy sites, which then act as electron-withdrawing groups with respect to protonation of the central naphthyl rings. For **2i**, a lower yield is also observed which is again attributed to greater protonation at positions distal to C1,C1'-bond cleavage site. Similarly, protonation of electron-donating methoxy groups at C3,C3' (**2j**), C6,C6' (**2k**) or C7,C7' (**2l**) is proposed to prevent the required C1,C1'-protonation. Electron–withdrawing groups directly attached to the binaphthyl core were not tolerated (**2m** and **2n**) likely due to reduced arene basicity.

A larger aromatic system (**2o**) resulted in drastically increased reactivity due to the increased basicity of the arene. However, this greater reactivity also resulted in uncontrollable side reactions reducing the yield of **2o**. In contrast, the dibenzofuran dimer did not produce **2p**, perhaps due to reduces basicity of the oxygen in the aromatic system. Replacing the hydroxy group with a methyl group (**2q**) resulted in no reaction showing the need for a more basic arene. For biphenyl analogs corresponding to **2r-2t**, no reaction was observed corresponding to the greater difficult of dearomatizing a benzene vs naphthalene ring. Use of higher temperature with the precursor to **2r** resulted only in cyclization to form the dibenzofuran (Supporting Information S24).

To investigate the mechanism, kinetic experiments were performed (Figure 3, Table 3 see Supporting Information Figure

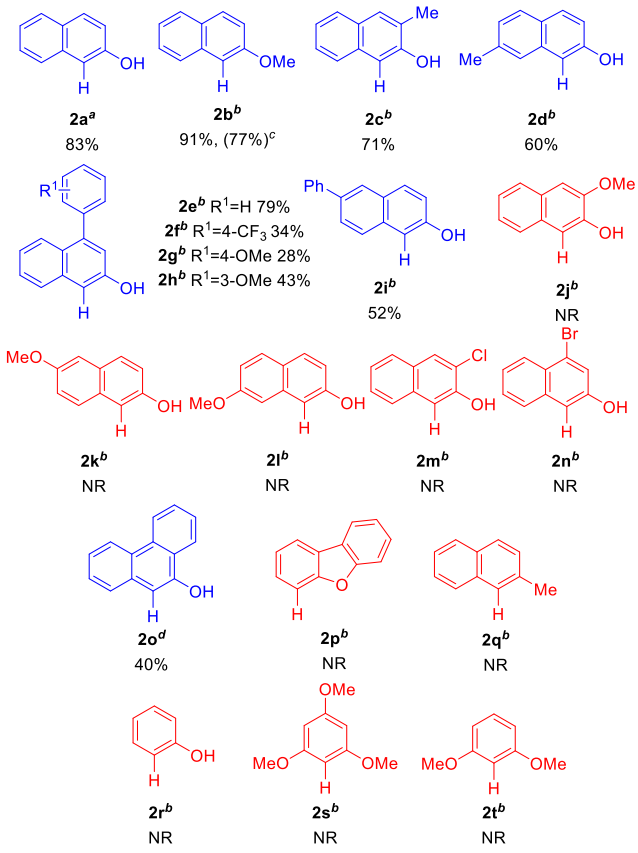


Figure 2. Product isolated yields obtained from the corresponding dimers (the C-H bond indicates cleavage site). ([a]0 °C. [b]rt. [c]Isolated 1 mmol scale [d]–78 °C)

S1–S4 for integrated rate plots). The reaction is first-order with respect to the substrate **1b** and second-order with respect to triflic acid. The second-order dependence on acid supports a double protonation of the substrate. Pd/C shows a zero-order dependence with a negligible decrease in rate at lower loadings. At the concentration examined, 2-ethylanthraquinone exhibits a negative first order dependence which may arise from sequestration of TfOH by protonation of the carbonyls thereby reducing the effective acid concentration. Kinetic isotope effects were not viable due to rapid H–D exchanage at multiple ring positions under these very acidic conditions.

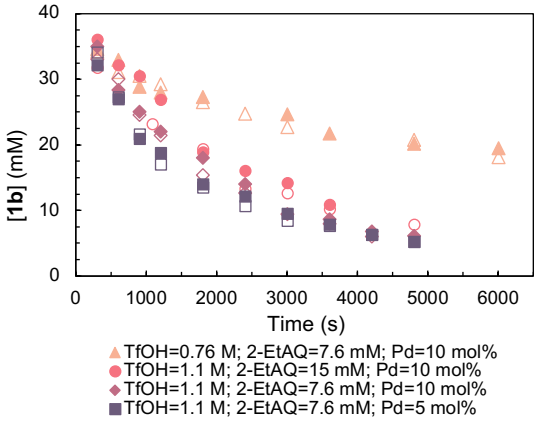


Figure 3. Plot of [**1b**] (mM) vs time (s) at different concentrations of reaction components.

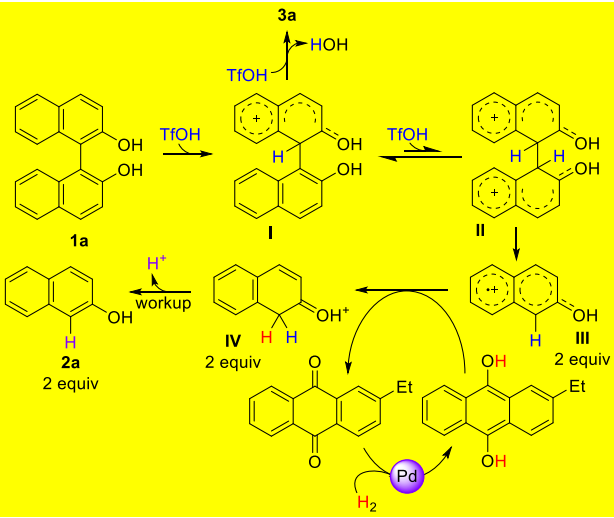
Table 3. Effect of Components on Rate

TfOH (M)	2-EtAQ (mM)	Pd (mol%)	Rate*10^4 (s^{-1})[a]
1.1	7.6	10	−4.13 ± 0.25
0.76	7.6	10	−2.08 ± 0.47
1.1	15	10	−3.17 ± 0.49
1.1	7.6	5	−3.92 ± 0.04

[a]Average of two runs

From these data, a mechanism is proposed (Scheme 3). First, triflic acid protonates one of the arenes to yield intermediate **I** which is likely to be spontaneous under these strongly acidic conditions.[13] Intermediate **I** can lead to product **3a** via an intramolecular displacement. Further, an equilibrium exists between **I** and **II** strongly favoring **I** especially at lower acid loading evidenced by increasing yields of **3a**. Following the second protonation event, intermediate **II** then undergoes homolytic cleavage promoted by dicationic repulsion[13, 20, 21] to generate two equivalents of radical cation **III**. HAT between **III** and 2-ethyl-9,10-dihydroxyanthracene generates **IV** and 2-ethylanthraquinone which is converted back to 2-ethyl-9,10-dihydroanthracene with Pd/C and H_2. Finally, deprotonation of **IV** provides **2a**. The kinetic data are consistent with either the second-protonation to form **II** or homolytic cleavage of **II** to **III** as the rate-limiting step.

Scheme 3. Proposed Mechanism



In summary, the use of hydrogen atom transfer catalysts to enable the reductive cleavage of biaryl bonds has been reported for the first time. The reactivity profile of a series of substrates and kinetic data support a dual protonation as a key step. Although the biaryl bond is the weakest C-C bond in these biaryl systems, it is still quite strong and its reductive cleavage is further complicated by the nonpolar nature of the bond. This HAT method provides new directions for reductively cleaving activated biaryl bonds.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.

Experimental procedures and NMR spectral copies (PDF)
FAIR data, including the primary NMR FID files, for compounds **1b-t, 2a-i, 2o.** (ZIP)

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ACKNOWLEDGMENT

We are grateful to the NSF (CHE2102626) for financial support of this research. Partial instrumentation support was provided by the NIH and NSF (1S10RR023444, CHE-1827457, 3R01GM118510-03S1, 3R01GM087605-06S1), as well as the Vagelos Institute for Energy Science and Technology. Dr. Charles W. Ross III (UPenn) is acknowledged for obtaining accurate mass data.

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