Diphenol Synthesis

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The Acetal Concept: Regioselective Access to *ortho,ortho*-Diphenols via Dibenzo-1,3-dioxepines**

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The biaryl C–C linkage is one of the most significant in chemistry, and has long[1] been a point of synthetic focus.[2] Nonetheless, some biaryl C–C linkages remain difficult to synthesize, usually for electronic reasons. One of these is the *ortho,ortho*-diphenol system (Figure 1), since transition-metal-catalyzed cross-coupling disfavors oxidative insertion

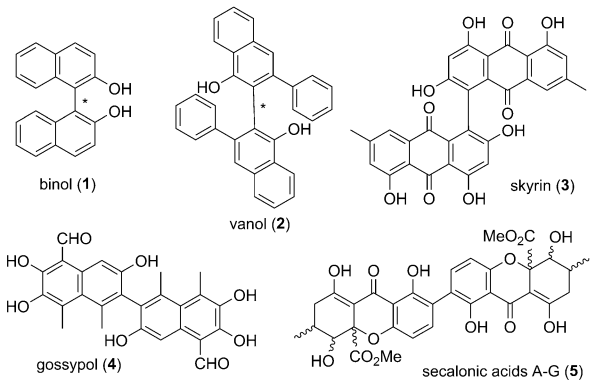
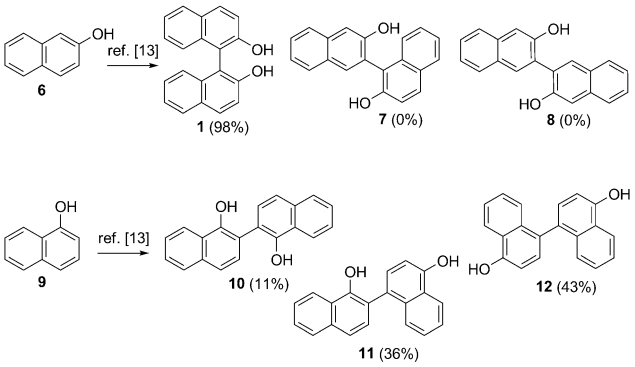


Figure 1. Representative *ortho,ortho*-diphenols.

ortho to a hydroxy or protected hydroxy group.[3] In eliminating the requirement for oxidative insertion into a carbon–(pseudo)halide bond, C–H activation has begun to show great promise as a more direct alternative,[4] particularly with the use of protected hydroxy groups as directing groups.[5]

We have an ongoing interest in the synthesis of the *ortho,ortho*-dihydroxybiaryl motif,[6] which is found in numerous structurally fascinating and biologically active natural products, drugs, and useful ligands for asymmetric catalysis. Examples of these include binol[7] (**1**, Figure 1) and vanol (**2**),[8] and the natural products skyrin (**3**)[9] and gossypol (**4**).[10] In particular, key synthetic targets of our group are the highly bioactive and widespread ergochrome family of mycotoxins, including the secalonic acids (**5**).[11] Despite the vast number of compounds known to contain this motif (see **8**, Scheme 1; over 18500 compounds identified recently in a Scifinder



Scheme 1. Comparison of the dimerization of 1- and 2-naphthol.

Scholar search), a general, reliable, regioselective method for their synthesis remains elusive. Herein, we describe a strategy providing access to a potentially wide range of synthetic targets of this type.

Existing transformations of phenolic substrates to form biaryls have generally been accomplished with oxidative coupling.[12] A drawback of this method is that it fails utterly with substrates that are not suited in terms of sterics or electronics, and results instead in either lack of reactivity or poor regioselectivity profiles. For example, 2-naphthol (**6**, Scheme 1) consistently forms binol (**1**) in dimerization reactions,[13] whereas 1-naphthol (**9**) with its greater radical stabilization reacts to form mixtures of 2,2′-, 2,4′-, and 4,4′-linked dimers (**10**, **11**, and **12**, respectively).[13]

The lack of a general method for the regioselective formation of dimeric and heterodimeric *ortho,ortho*-diphenols (and derivatives thereof) is therefore a shortcoming in the range of existing synthetic methodologies. One possibility to address the poor selectivity is the application of an intramolecular tether, which would limit the reactivity to physically accessible sites of the substrate. Inspired by elegant methods for biaryl coupling relying on temporary intramolecular tethers, including Bringmann's "lactone concept" (Scheme 2),[14] and the work of Lipshutz,[15] we envisioned that the use of a tether to impose *ortho* regioselectivity upon the reaction of phenolic substrates would provide access to target molecules with a 1,1′-dihydroxy-2,2′-biaryl motif. The method would involve the acetal linkage of the two phenolic moieties, followed by C–C bond formation, and finally removal of the linker.

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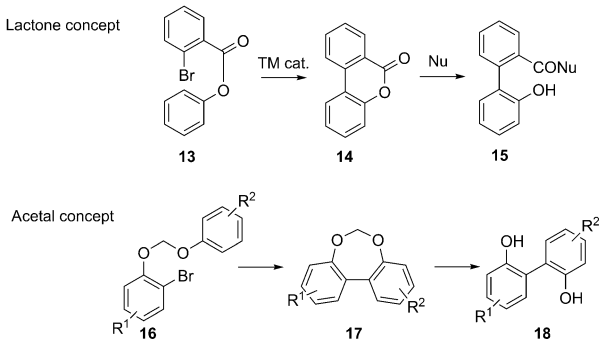
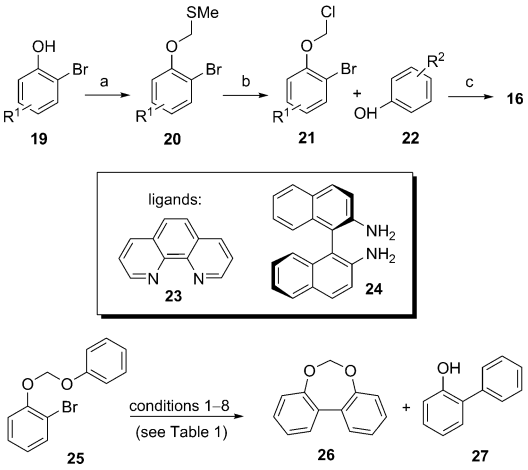


Scheme 2. The lactone concept and the acetal concept. TM cat. = transition-metal catalyst.

Owing to the ready accessibility of the substrates[16] and the simplicity of the reaction reagents and conditions, we felt we had ample time to attempt construction of the biaryl connection by a newly described alternative to transition-metal-catalyzed coupling and C–H functionalization. The recent discovery of a biaryl-coupling methodology involving radical anion intermediates and utilizing diamine ligands and *tert*-butoxide base, with no need for metal-containing substrates or catalysts, has aroused considerable interest (Scheme 3).[17] The methodology involves coupling of aryl iodides or bromides with pyridine and pyrazine,[17a] benzene,[17b] or substituted arenes.[17c–e] The mechanism appears to follow a homolytic radical aromatic substitution (HAS) pathway.[18]

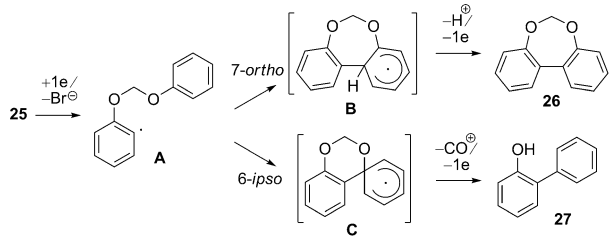
The *ortho*-bromo-substituted methylene diphenyl ether substrates were readily synthesized from commercially available phenols and their *ortho*-brominated derivatives, exploiting a facile and high-yielding two-step protocol previously reported by Guillaumet and co-workers:[16] The bromo-substituted phenol **19** was reacted under basic conditions with chloromethyl methyl sulfide to yield **20**, which was



Scheme 3. Synthesis of substrates; Ligands tested; Optimization. Conditions for the conversions at the top: a) NaH, DMF, chloromethyl methyl sulfide; b,c) SO_2Cl_2, CH_2Cl_2, solvent removal; then **22**, K_2CO_3, DMF. Reaction conditions for the conversion at the bottom are given in Table 1.

subsequently converted to the chloride with sulfuryl dichloride and reacted with a second phenol, **22**, in a pseudo-one-pot reaction, yielding a range of acetal-linked compounds **16**. Yields were consistently good to excellent.

We then optimized the C–C bond formation with the simple bromo-functionalized biphenyl acetal **25** (Scheme 4), which gave 1,3-dioxepine **26** as the product, alongside 2-



Scheme 4. Competing cyclizations to dioxepine **26** and phenol **27**.

phenylphenol (**27**) as a byproduct. Testing several solvents for this reaction under microwave irradiation, we found that pyridine was superior to mesitylene, toluene, and collidine (Table 1, entries 1–4).[17e] An increase in temperature to 120 °C gave a better conversion (77 % by HPLC analysis, 49 % yield of isolated product, entry 5). Reaction for a longer time at a reduced temperature (80 °C for 240 min, entry 6) resulted low conversion. A decrease in the number of equivalents of base gave a lower conversion (69 %, entry 7). Lastly, application of a novel ligand, (*R*)-(1,1′-binaphthyl)-2,2′-diamine (**24**) (entry 8), proved to also promote the reaction, although with an undesirable selectivity profile.

The isolation of 2-phenylphenol (**27**) is noteworthy, in that it not only supports the mechanistic hypothesis of Studer and Curran,[18] but provides insight into the formation of the seven-membered ring, which can be entropically disfavored. In light of the previous observations of competing *ipso* cyclizations under these same conditions,[17e] it seems reasonable that, rather than the desired 7-*ortho* cyclization to **26** via intermediate **B** (Scheme 4), a competing 6-*ipso* cyclization can progress to **27** through intermediate **C**; the oxidation of the cyclohexadienyl radicals (rearomatization) can occur stepwise by either electron transfer then proton transfer (**B**)/deformylation (**C**), or by the alternative sequence of

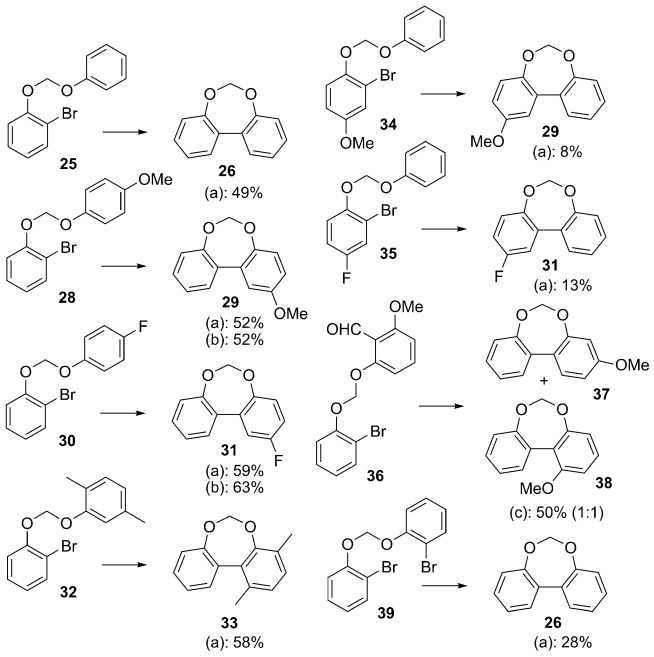
Table 1: Reaction optimization.[a]

Entry	Solv.[b]	KO*t*Bu [equiv]	Ligand (mol %)	*T* [°C]	*t* [min]	Conversion [%][c] **25**	**26**	**27**
1	Tol.	3.0	**23** (40)	100	120	96	4	0
2	Mes.	3.0	**23** (40)	100	120	86	12	2
3	Pyr.	3.0	**23** (40)	100	120	15	68	17
4	Coll.	3.0	**23** (40)	100	120	47	44	9
5	*Pyr.*	*3.0*	***23*** *(40)*	*120*	*120*	*15*	*77*	*8*
6	Pyr.	3.0	**23** (40)	80	240	60	33	7
7	Pyr.	1.0	**23** (40)	120	120	19	69	11
8	Pyr.	3.0	**24** (40)	120	120	0	51	49

[a] Heating by means of microwave irradiation. [b] Solvents: Tol. = toluene, Mes. = mesitylene, Pyr. = pyridine, Coll. = collidine. [c] Conversion values, determined by HPLC analysis of the reaction mixtures.

events.[18] The scission of the O–C bond under radical conditions is known and can be employed for synthetic purposes.[19]

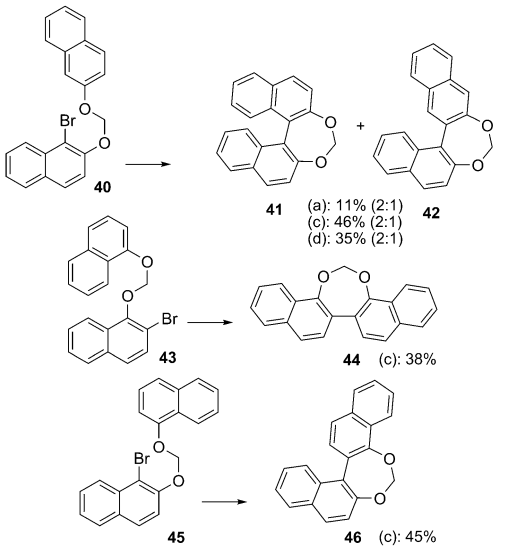
We next investigated the scope of the reaction with substituted diphenyl acetal derivatives, utilizing the optimized conditions (Scheme 5). Reaction of acetals with either



Scheme 5. Scope of the reaction with diphenyl acetals. Reaction conditions: KO*t*Bu (3 equiv), 1,10-phenanthroline (40 mol%), pyridine, and microwave irradiation at 120°C for a) 120 min, b) 6 min, c) 240 min.

electron-donating or electron-withdrawing substituents on the arene not bearing the bromide proved favorable, forming the desired dibenzo-1,3-dioxepines (examples **28** and **30**) with complete regioselectivity. For the *para*-methoxy-substituted acetal **28**, reaction times of 6 and 120 min gave the same results. Even the reaction of the sterically demanding 3,5-dimethylphenyl acetal **32** proved facile. Substitution on the bromo-functionalized ring of the diphenyl acetal (examples **34** and **35**) was less well-tolerated; the substrates were completely consumed, complex mixtures formed, and the 1,3-dioxepines were obtained in poor yields. The aldehyde functionality was not tolerated under the reaction conditions,[20] and products **37** and **38** were formed in a 1:1 ratio. This outcome may have resulted from either initial radical deformylation and nonselective cyclization of the resulting *m*-methoxylated intermediate, although the ratio of products is not in accord with the *ortho* selectivities normally observed for HAS reactions.[18] An alternative explanation is 6-*exo* cyclization of the type leading to intermediate of type **C** (Scheme 4), followed by a nonselective rearomatizing C-migration. Lastly, the reaction also proceeded with the symmetrical bis-bromophenyl acetal **39**, although in a much less satisfactory yield (28%). This result indicates that the loss of either bromonium ion and electron transfer, or alternatively, a bromine radical, may also be an alternative final step in the mechanism.

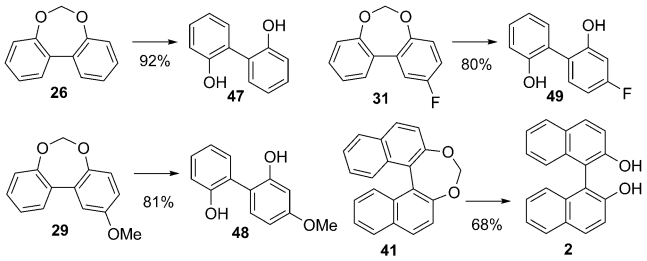
Reaction of the binaphthyl acetals (**40**, **43**, and **45**, Scheme 6) proceeded much more slowly under the reaction conditions. Acetal **40**, derived from 1-bromo-2-naphthol and 2-naphthol, cyclized to form a mixture of symmetrical and



Scheme 6. Scope of the reaction with dinaphthyl acetals. Reaction conditions: KO*t*Bu (3 equiv), 1,10-phenanthroline (40 mol%), pyridine, microwave irradiation at 120°C for a) 120 min, c) 240 min, d) as in (c), but with (*R*)-(1,1′-binaphthalene)-2,2′-diamine (40 mol%) as catalyst.

unsymmetrical 1,3-dioexpines, **41** and **42**, in moderate yield and a consistent 2:1 ratio. Acetal **43**, a derivative of 2-bromo-1-naphthol and 1-naphthol, likewise cyclized slowly, giving the unusual 1,3-dioxepine **44**. The unsymmetrical dinaphthyl acetal **45**, from 1-bromo-2-naphthol and 1-naphthol, gave access to the unsymmetrical dioxepine **46**. Interestingly, this was the only dioxepine in which the methylene protons were observed to give a $J_{A,A}$ system in the ^{1}H NMR spectrum. It was furthermore found that the use of the chiral diamine **24** as the catalyst did not impart enantioselectivity in the formation of **41** (binol acetal), supporting the suggestion of Studer and Curran that the diamine functions as a radical initiator and is not directly involved in the C–C bond-forming step.[18]

The hydrolysis of methylene acetals is known to require relatively harsh conditions.[21] We nonetheless found that heating the 1,3-dioxepines in ethanolic hydrochloric acid solutions gave the desired 2,2′-diphenolic products in good to excellent yields (Scheme 7). Diphenol-derived dioxepine **26** hydrolyzed to 2,2′-diphenol **47** in excellent yield (92%), and the methoxy and fluoro derivatives, **29** and **31**, reacted to give their respective diphenol products, **48** and **49**. The hydrolysis of binol-acetal (dioxepine **41**) to binol (**2**, identical with commercially available *rac*-binol) was notably rapid (3 h), most probably due to the steric strain intrinsic to this system. One exception was bis(1-naphthyl) acetal **44**, which appears to possess an unusual degree of stability to Brønsted acid, and did not react under these conditions.



Scheme 7. Hydrolysis of selected dibenzo-1,3-dioxepines. Reaction conditions: aq. HCl/EtOH (1:5), 50 °C, 4–36 h.

Further studies into the scope and application of this reaction are underway in our laboratories, and will be reported shortly. We believe that the "acetal concept" will prove to be a generally applicable solution to the regioselective synthesis of *ortho*,*ortho*-diphenols.

Experimental Section

General procedure for the synthesis of dibenzo-1,3-dioxepines**:** A 10 mL microwave vial was charged with the bromo-substituted substrate (0.25 mmol) and anhydrous pyridine (1.5 mL), followed by 1,10-phenanthroline (18 mg, 0.10 mmol) and potassium *tert*-butoxide (84 mg, 0.75 mmol). The vial was capped and the atmosphere cautiously removed with stirring under vacuum, then replaced with argon (repeated three times). The reaction mixture was then heated to the stated temperature for the stated time by means of microwave irradiation for 120 min. After this time, the blood-red reaction mixture was allowed to cool to room temperature, then filtered/washed through a short column of silica gel with ethyl acetate (50 mL) as eluent. The volatiles were removed under reduced pressure; the resulting crude was purified by column chromatography on silica gel with cyclohexane/dichloromethane mixtures, yielding the dibenzo-1,3-dioxepine.

General procedure for the hydrolysis of dibenzo-1,3-dioxepines to *ortho*,*ortho*-biphenols**:** To a stirred solution of the dioxepine in ethanol (0.10 M) was added dropwise concentrated $HCl_{(aq.)}$ (0.20 mL per mL ethanol). The cloudy reaction mixture was then heated to 50 °C in an oil bath, then the flask was sealed with a septum. The reactions were monitored by thin-layer chromatography for consumption of starting material; it was noted that when the substrate had been consumed the reaction mixtures was optically clear. Reaction times varied greatly, depending on the nature of the substrate. When the reaction was complete, silica gel was added to the flask and the volatiles were removed under reduced pressure, then the crude was purified by column chromatography on silica gel with cyclohexane/ethyl acetate mixtures, yielding the 2,2′-diphenol.

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