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Divergent Reaction Pathways for Phenol Arylation by Arynes: Synthesis of Helicenes and 2-Arylphenols

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Abstract

Two reactions of phenols with arynes have been developed. If LiTMP base is employed, arynes generated from aryl chlorides react with phenols to form helicenes. *o*-Arylation of phenols can be achieved by employing *t*BuONa base in the presence of AgOAc. Direct arylation of binol was achieved leading to the shortest pathway to *o,o'*-diarylbinols.

2-Arylphenol functionality can be found in organocatalysts, sensors, phosphite ligands, and biologically active substances.¹ The most common methods for synthesis of these structures involve cross-coupling of an organometallic reagent with an aryl halide or pseudohalide.^{1a,2} In addition to several step synthesis of both coupling components, the phenol moiety usually has to be protected. Shorter synthetic pathways to 2-arylphenols can be achieved by employing transition-metal catalyzed C-H bond functionalization methodology.³ First palladium-catalyzed phenol *ortho*-arylations were reported by Miura.^{3a} However, in many cases polyarylation was observed. Subsequently, Bedford published a method for rhodium-catalyzed arylation of 2-substituted phenols.^{3b} More recently, Bedford, Dong, and Liu have shown that phenols possessing ester and carbamate directing groups can be arylated under palladium catalysis by aryl halides or simple arenes.^{3c-e} Gevorgyan has shown that selective phenol derivative *ortho*-arylation is possible by employing a silicon-based tether that can be subsequently removed.^{3f} Gaunt has reported *para*-arylation of phenol ethers by diaryliodonium salts.^{3g} Direct intermolecular *ortho*-arylation of unprotected phenols by aryl chlorides has not yet been disclosed. We report here a method for base- and silver-promoted phenol direct *ortho*-arylation by aryl chlorides that proceeds via benzyne mechanism. A one-step transition-metal-free synthesis of helicenes is also disclosed.

Phenol *O*-arylation can be accomplished by benzyne.⁴ Minor amounts of *C*-arylation products may accompany diaryl ethers.⁴ Since the ratio of *C*- vs. heteroatom arylation can be tuned by changing reaction solvent,^{5a-b} we decided to explore phenol *o*-arylation. Arynes can be generated from silyl aryl triflates under nearly neutral conditions at room temperature.⁶ These starting materials are expensive and only a few of them are commercially available. Consequently, we used readily accessible and cheap aryl chlorides as aryne sources. Two different reaction conditions were investigated for phenol arylation. The first set of conditions employs lithium 2,2,6,6-tetramethylpiperidide (LiTMP) base. These conditions are based on our earlier report for heterocycle arylation by aryl halides.^{5a} The second set of conditions involves an alkali metal alkoxide base in dioxane and is based on intramolecular arylation of phenol derivatives.^{5c} Very different reaction outcomes were observed depending on the conditions used.

If a solution of phenol and chlorobenzene in THF was treated by TMPLi, diphenyl ether was formed together with a hydrocarbon in 4/1 ratio (Table 1, entry 1). Spectroscopic analysis showed that hydrocarbon product is benzo[c]phenanthrene (tetrahelicene). Helicenes have been used in asymmetric catalysis, as molecular machines, and as organic electronic materials.⁷ Their syntheses are typically lengthy,⁸ and one-step access to helicenes from simple, commercially available starting materials would make these interesting structures more available. For example, parent hexahelicene has been prepared in six steps by employing ring-closing metathesis.^{8c} Consequently, we decided to optimize the helicene formation and investigate the reaction mechanism. Optimization of the reaction conditions showed that increase of phenol/chlorobenzene ratio to 1/4 and use of mixed pentane/THF solvent resulted in 80% conversion to tetrahelicene (entry 6).

Examples of the helicene synthesis are presented in Table 2. Reaction of phenol with chlorobenzene affords a 67% isolated yield of tetrahelicene (entry 1). If 2-*t*-butylphenol is reacted with chlorobenzene, 5-*t*-butyltetrahelicene is obtained in 48% yield (entry 2). 5,6-Dimethyltetrahelicene is produced from 2,3-dimethylphenol in 58% yield (entry 3). 2-Phenylphenol is converted to 5-phenyltetrahelicene in 65% yield (entry 4). Hindered 2,6-diisopropylphenol is reactive and 5,8-diisopropyltetrahelicene was formed in 40% yield (entry 5). 6-Trifluoromethyltetrahelicene can be synthesized in 40% yield (entry 6). 3-*t*-Butylphenol can be converted to 6-*t*-butyltetrahelicene in 51% yield (entry 7).

A TBS-protected resorcinol afforded the product in a good yield (entry 8). The reaction of 2,6-dimethylphenol with 1-chloronaphthalene resulted in formation of two isomeric hydrocarbons in 2.1/1 ratio and 60% yield. The major product was hexahelicene **11** that could be isolated in 26% yield by fractional crystallization of the isomer mixture (Scheme 1).

Analysis of the reaction products shows that helicenes are formed by the reaction of two molecules of aryl chloride with one molecule of phenol. Informative results were obtained in the reaction of 3-*t*-butylphenol with 1.6 equiv chlorobenzene (Scheme 2). Benzocyclooctadienone **12** was obtained in 61% yield. If 3 equiv of chlorobenzene and 4.2 equiv of LiTMP were employed, structure **13** was isolated in 64% yield. Compound **12** could be converted to **13** by reaction with 2 equiv of PhCl in the presence of 3.2 equiv LiTMP. Both **12** and **13** can be transformed to *t*-butyltetrahelicene **8** as shown in Scheme 2. Direct reaction of 4 equiv chlorobenzene with 3-*t*-butylphenol in the presence of 6 equiv LiTMP affords **8** (entry 7, Table 2). These experiments show that **12** and **13** are competent intermediates *en route* to **8**. In addition, the reaction of 4-hydroxybiphenyl with chlorobenzene afforded **14** which cannot easily aromatize by elimination. X-Ray crystallographic analysis of *O*-methyl derivative of **14** showed that hydroxyl and phenyl groups are in *cis* arrangement.

The following reaction mechanism is proposed (Scheme 3). Reaction of phenol with benzyne generated from chlorobenzene forms a benzocyclobutene **15**. Ring-opening affords **16** which undergoes another reaction with benzyne to form **17**. Subsequent opening of the strained four-membered ring in **17** gives a ten-membered ring ketone **18**. Intramolecular nucleophilic attack followed by dehydration affords tetrahelicene **2**. Intermediates related to **16** and **19** have been isolated and characterized (**12**, **13**, and **14**, Scheme 1). Benzene cycloaddition with benzyne producing a benzocyclobutane derivative that subsequently ring-opens to give benzocyclooctatetraene in low yield has been reported showing the viability of intermediates such as **15** and **17**.⁹

As described above, use of LiTMP base afforded no detectable phenol *C*-arylation. The application of *t*BuONa in dioxane gave minor amounts of *C*-arylation (Table 3). In enolate

chemistry, the *C*- vs. *O*-functionalization ratios are influenced by the counterion,¹⁰ and *C*-functionalization of hexafluoroacetylacetone can be achieved via its Ag salt.^[11a] Thus, addition of 0.5-1 equiv AgOAc resulted in a good selectivity for *C*-arylation. The optimized conditions include AgOAc additive, 155 °C, dioxane solvent, and NaOtBu base.

The arylation scope is presented in Table 4. Phenol can be either mono- or diarylated in good yield depending on phenol/chlorobenzene ratio (entries 1 and 2). Introduction of 3-fluorophenyl substituent is possible (entry 3). Reaction of phenol with 2-chloroanisole affords the 3-methoxyphenylated derivative (entry 4).^{11b} Substituted phenols, such as 3-methylphenol (entry 5), 4-hydroxybenzophenone (entry 6), 1-naphthol (entry 7), and 2-naphthol (entry 8) can be phenylated in good to excellent yields.

The reaction is surprisingly functional group tolerant despite the use of strong *t*-butoxide base. Thus, fluoride (entry 3), ether (entry 4), ketone (entry 6), trifluoromethyl (entry 9), ester (entry 10), and cyano groups (entry 11) are tolerated. Arylation of 2-naphthol (entries 8-11) does not require AgOAc additive. Phenylation of 2-naphthol on a 10 mmol scale afforded product in 77% yield (entry 8).

Arylated binol derivatives are used as organocatalysts.^{1a} Their syntheses require several steps from relatively expensive starting materials.^{1a} Direct *C*-arylation of binol is the shortest possible route to such compounds. This pathway should also allow introduction of two different aryl groups into binol moiety, thus allowing access to structurally diverse organocatalysts. Diarylation of binol with excess chlorobenzene afforded **21** in 51% yield (Scheme 4). A two-step synthesis of an unsymmetrical diarylbinol was also achieved. Thus, binol was phenylated to afford 3-phenylbinol **22** in 67% yield. Subsequently, **22** was arylated by 1-chloro-3-fluorobenzene to afford 3,3'-diarylbinol **22** in 60% yield. Additionally, arylation of enantiopure (*R*)-binol with 3-chloroanisole afforded product **24** in 50% yield and 95% ee, showing the applicability of the method to synthesis of enantioenriched organocatalysts. In conclusion, we have described two reactions of phenols with arynes. If LiTMP base is employed, arynes generated from aryl chlorides react with phenols to form helicene derivatives. If *t*BuONa base is used in dioxane at elevated temperature in the presence of AgOAc, selective *o*-arylation of phenols can be achieved. Diarylation of binol was demonstrated resulting in the shortest pathway to *o,o'*-diarylbinols. Enantiopure binol was *o*-arylated by 3-chloroanisole affording 3-(3-methoxyphenyl)binol in 95% ee.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Hexahelicene Synthesis

Scheme 2.
Reaction Intermediates

Scheme 3.
Reaction Mechanism

Scheme 4.
Binaphthol Arylation

Table 1
Optimization of Reaction Conditions^a

entry	PhOH/PhCl/LiTMP	solvent	1/2/conv
1	1/2/3.6	THF	4/1/32%
2	1/2/3.6	Et ₂ O	3/1/21%
3 ^b	1/2/3.6	C ₅ H ₁₂	1/7/35%
4	1/2/3.6	C ₅ H ₁₂ /THF 20:1	1/40/52%
5	1/2/3.6	C ₅ H ₁₂ /THF 50:1	1/50/65%
6	1/4/6	C ₅ H ₁₂ /THF 50:1	1/50/80%

^aVolume of solvent 1 mL, 0.25 mmol scale, 24 h, 25 °C. Conversion by GC analysis. See Supporting information for details.

^bAt 40 °C.

Table 2

Helicene Synthesis^a

entry	phenol	helicene	yield, %
1	PhOH	2	67
2	2- <i>t</i> Bu-phenol	3	48
3	2,3-di-Me-phenol	4	58
4	2-Ph-phenol	5	65
5	2,6-di- <i>i</i> Pr-phenol	6	40
6	3-CF ₃ -phenol	7	40

entry	phenol	helicene	yield, %
7	3- <i>t</i> Bu-phenol		51
8	3-TBSO-phenol		52

^aScale: 0.5 mmol. Yields are isolated yields. See SupportingInformation for details.

Table 3
Optimization of Phenol Arylation^a

entry	PhCl/PhOH/base	solvent, T	1/20/conv
1	2/1/3.9/LiTMP	Et ₂ O, 25 °C	50/<1/32%
2	2/1/3.9/ <i>t</i> BuOK	dioxane, 110 °C	9/1/91%
3	2/1/3.9/ <i>t</i> BuONa	dioxane, 155 °C	7/1/87%
4 ^b	2/1/3.9/ <i>t</i> BuONa	dioxane, 155 °C	1/30/87%
5 ^c	2/1/3.9/ <i>t</i> BuONa	dioxane, 155 °C	1/15/65%

^aSolvent (1 mL), 0.25 mmol scale, 24 h. Conversion by GC analysis.

^bAdditive: 1 equiv AgOAc.

^cAdditive: 0.1 equiv AgOAc.

Table 4

Phenol Arylation^a

entry	phenol	ArCl	product	yield, %
1	phenol	PhCl		78
2	phenol	PhCl		60
3	phenol	1-Cl-3-FC ₆ H ₄		72
4 ^b	phenol	2-Cl-1-MeOC ₆ H ₄		64
5	3-Me-phenol	PhCl		80
6	4-OH-benzo-phenone	PhCl		58
7	1-naphthol	PhCl		82

entry	phenol	ArCl	product	yield, %
8 ^c	2-naphthol	PhCl		80 77 ^d
9 ^c	2-naphthol	3-Cl-1-CF ₃ C ₆ H ₄		74
10 ^c	2-naphthol	3-Br-1-tBuO ₂ CC ₆ H ₄		66
11 ^c	2-naphthol	3-Cl-1-CNC ₆ H ₄		65

^aScale: 0.5 mmol, 48-96 h, 0.5-2 equiv AgOAc, 1.6-5/1/3.6-8ratio of ArCl/phenol/base. Yields are isolated yields.

^bCrude: 9/1 isomer mixture. Yield of pure major isomer.

^cNo AgOAc.

^dReaction scale: 10 mmol.