

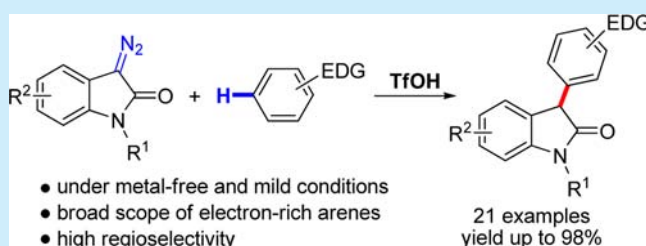
Facile Synthesis of 3-Aryloxindoles via Brønsted Acid Catalyzed Friedel–Crafts Alkylation of Electron-Rich Arenes with 3-Diazooxindoles

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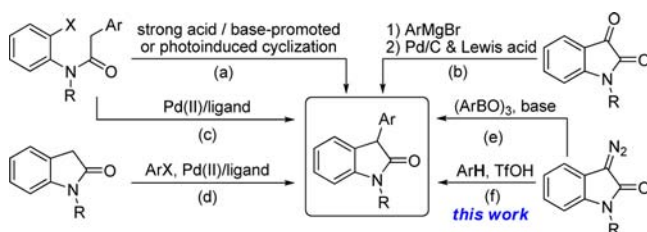
S Supporting Information

ABSTRACT: A simple metal-free method for the synthesis of 3-aryloxindoles via Brønsted acid catalyzed aromatic C–H functionalization of electron-rich arenes with 3-diazooxindoles is developed. In the presence of a catalytic amount of TfOH, a series of 3-aryloxindoles are synthesized as single regioisomers in good to excellent yields. This transformation is proposed to proceed through acid-catalyzed protonation of 3-diazooxindoles into diazonium ions followed by Friedel–Crafts-type alkylation of arenes.



3-Aryloxindoles are widely used precursors for the synthesis of different types of 3,3-disubstituted oxindoles and indolines, which constitute the core of a large number of biologically active natural products and synthetic pharmaceutical agents.^{1,2} Over the past few decades, an array of methods have been developed for the preparation of 3-aryloxindoles. The classical ones include strong acid-promoted intramolecular Friedel–Crafts cyclization,³ strong base-promoted cyclization,⁴ or photoinduced cyclization of α -haloacetanilides (Scheme 1,

Scheme 1. Strategies for the Synthesis of 3-Aryloxindoles



path a).⁵ In recent years, the reaction of aryl Grignard reagents with isatins followed by Pd/C or strong Lewis acid-promoted reductive deoxygenation has become the most generally applied method for the synthesis of 3-aryloxindoles (Scheme 1, path b).^{2b,e,6} On the other hand, palladium-catalyzed intramolecular α -arylation of amides⁷ (Scheme 1, path c), intermolecular α -arylation of oxindoles with aryl halides⁸ (Scheme 1, path d), or α -arylation of 3-diazooxindole with arylboroxines⁹ (Scheme 1, path e) has also been developed as an elegant protocol for the synthesis of 3-aryloxindoles. Among all of these methods, however, harsh reaction conditions (strong acidic or basic conditions) or the use of air-sensitive metal reagents or

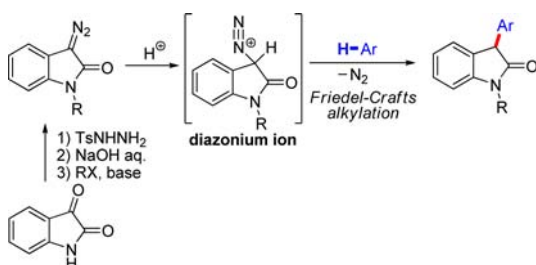
transition-metal catalysts are generally required. As a result, the development of simple and convenient methods for the synthesis of 3-aryloxindoles that can be implemented under mild conditions without the use of metal reagents or transition-metal catalysts is highly desirable. Herein, we describe the facile synthesis of 3-aryloxindoles via a Brønsted acid-catalyzed Friedel–Crafts type alkylation of arenes with 3-diazooxindoles (Scheme 1, path f).

As an important class of reagents, diazo compounds have been widely applied to different types of organic transformations. Among them, it has been a well-established process that diazo compounds undergo protonation to afford diazonium ion under Brønsted acid catalysis.¹⁰ This process has been involved in the earliest application of diazo compounds for esterification of carboxylic acids¹¹ and has been applied to O–H insertions of water or alcohols¹² as well as certain types of rearrangement reactions.¹³ Surprisingly, except for these achievements, such processes did not find further synthetic applications in organic chemistry and have been generally considered as the major competitive reactions in transformations where Brønsted acid catalysts were used to activate electrophiles to react with diazo compounds.¹⁴ As part of our research program aimed at exploring the unique reactivity of 3-diazooxindole for new transformations,¹⁵ we envisioned that a diazonium ion generated from 3-diazooxindole in the presence of a Brønsted acid would undergo Friedel–Crafts-type alkylation with arenes,¹⁶ therefore providing a metal-free strategy for the preparation of 3-aryloxindoles starting from isatins (Scheme 2).¹⁷ However, since 3-

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Scheme 2. Friedel–Crafts Alkylation of Arene with 3-Diazoindole via Diazonium Ion Intermediate



diazooindole is a relatively less reactive diazo source,¹⁸ it remains unclear whether the desired diazonium ion intermediate would be efficiently generated under Brønsted acid catalyzed conditions, and the generated diazonium ion may undergo competitive hydrolysis and homocoupling, therefore affecting the efficiency in affording the desired alkylation product. On the other hand, when substituted arenes are used as the substrates, the regioselectivity during the alkylation process may also be a problem.

With these concerns, we started our initial investigation by choosing *N*-benzyl-3-diazoindole **1a** and toluene as the substrates wherein toluene was also used as the solvent. When 50 mol % of methanesulfonic acid (MsOH) ($pK_a = -2.6$) was used as the catalyst, 3-aryloxindole **3a** was afforded in 61% yield along with the formation of hydrolysis product as well as O–H insertion product from MsOH as the major side products (Table 1, entry 1). With this encouraging result, other Brønsted

Table 1. Optimization of the Reaction Conditions^a

entry	cat.	X	solvent	equiv of 2a	yield ^b (%)
1	MsOH	50	toluene		61
2	TfOH	50	toluene		98
3	CSA	50	toluene		<5
4	TsOH	50	toluene		<5
5	none		toluene		<5
6	TfOH	20	toluene		96
7	TfOH	20	DCM	5.0	80
8	TfOH	20	CHCl ₃	5.0	83
9	TfOH	20	DCE	5.0	87
10	TfOH	20	DCE	3.5	62
11 ^c	TfOH	20	DCE	5.0	70

^aReactions were conducted by adding **1a** (0.2 mmol) in 1 mL of the solvent to the mixture of **2a** and catalyst in 0.7 mL of the solvent via syringe pump over 30 min. ^bIsolated yield. ^cWith the addition of 100 mg of 4 Å MS.

acid catalysts were further evaluated. When more acidic triflic acid (TfOH) ($pK_a = -14$) was used as the catalyst, **3a** was afforded in 98% yield as a single regioisomer (Table 1, entry 2).^{19,20} The use of weaker Brønsted acids such as camphorsulfonic acid (CSA) ($pK_a = 1.2$) or *p*-toluenesulfonic acid (TsOH) ($pK_a = 3.9$) as catalysts failed to decompose **1a**, and the formation of **3a** was not observed (Table 1, entries 3

and 4). These results indicated that the acidity of Brønsted acids is crucial for this transformation to successfully proceed. Control experiments without the addition of TfOH did not give any desired product (Table 1, entry 5). By applying TfOH as the catalyst, further optimizations were conducted. Reducing the loading of TfOH from 50 to 20 mol % still gave **3a** in very high yield (Table 1, entry 6). This reaction also run smoothly when 5.0 equiv of toluene was used in different halogenated solvent, while 1,2-dichloroethane (DCE) was the best solvent to give **3a** in 87% yield (Table 1, entries 7–9). However, further reducing the amount of toluene from 5.0 to 3.5 equiv resulted in a much reduced yield (Table 1, entry 10). The addition of 4 Å molecular sieves caused a declined yield of **3a** (Table 1, entry 11), which indicated that the existence of slight amount of water might be beneficial to this reaction. Moreover, all reactions were carried out in open air with AR-grade solvents, which means this transformation is very reliable and easy to operate.

With the optimized reaction conditions in hand, the scope of 3-diazoindoles for this TfOH-catalyzed aromatic substitution reaction was first investigated by choosing toluene as the arene source as well as the solvent. In addition to *N*-benzyl-3-diazoindole **1a**, *N*-methyl-3-diazoindole also reacted with toluene smoothly to afford the desired alkylation product in good yield (Table 2, entries 1 and 2). An ester substituent on

Table 2. Scope of 3-Diazoindoles^a

entry	R ₁	R ₂	3	yield ^{b,c} (%)
1	Bn	H	3a	96
2	Me	H	3b	66
3	CO ₂ Et	H	3c	78
4	Bn	4-Cl	3d	74
5	Bn	5-Cl	3e	68
6 ^d	Bn	6-Cl	3f	60
7	Bn	5-Br	3g	85
8	Bn	5-Me	3h	74
9	Bn	6-F	3i	72

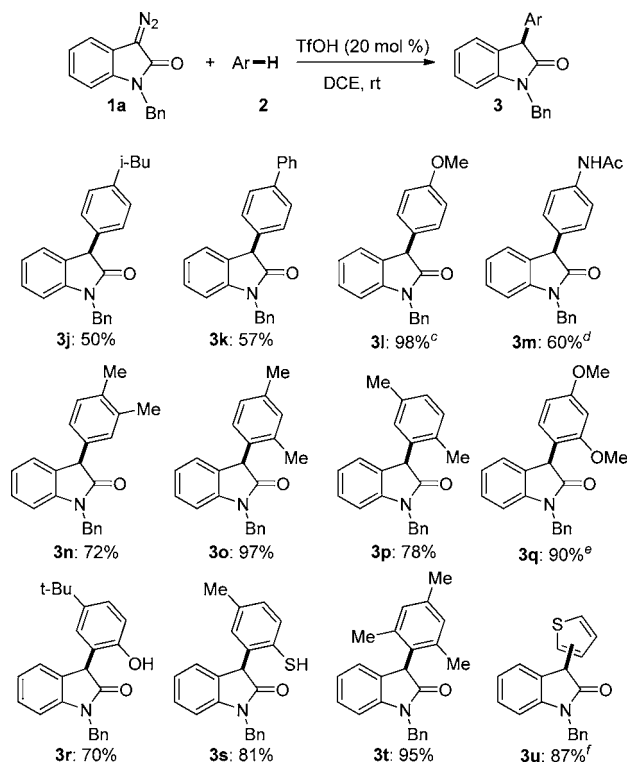
^aAll reactions were conducted by adding **1** (0.2 mmol) in 1 mL of toluene to the mixture of TfOH (20 mol %) in 0.7 mL of toluene via syringe pump over 30 min, and the reaction mixture was stirred for another 10 min. ^bIsolated yield. ^cUnless otherwise noted, the regioisomeric ratio (*para*/*ortho*) is larger than 95:5 as determined by ¹H NMR of the crude mixture. ^d*Para*/*ortho* = 93:7.

nitrogen atom of 3-diazoindoles was also applicable to this transformation, providing the desired product in 78% yield (Table 2, entry 3). *N*-Benzyl-3-diazoindoles bearing different substituents on the aromatic ring were also tested. With 4- or 5-chloro-substituted 3-diazoindoles as the substrates, the desired alkylation products were afforded in good yields (Table 2, entries 4 and 5). 5-Methyl- or 5-bromo-substituted 3-diazoindoles gave the desired products in much higher yields (Table 2, entries 7 and 8). Substrates bearing halogen substituents at 6-position also underwent the desired alkylation reaction, however, with slightly decreased efficiency (Table 2,

entries 6 and 9). For most cases, excellent regioselectivities (*para/ortho* > 95:5) were observed.

The scope of arenes was further investigated by choosing DCE as the solvent. When isobutyl-substituted benzene or biphenyl was used as the substrate, the desired *para*-substituted products were produced exclusively in good yields (Scheme 3, 3j and 3k).

Scheme 3. Scope of Arenes^{a,b}



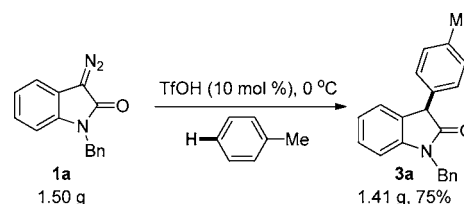
^aUnless otherwise noted, all reactions were conducted by adding **1a** (0.2 mmol) in 1 mL of DCE to the mixture of **2** (5.0 equiv) and TfOH (20 mol %) in 0.7 mL of DCE via syringe pump over 30 min, and the reaction mixture was stirred for another 10 min. ^bIsolated yields. ^c*Para/ortho* = 87:13. ^d2 equiv of TfOH was used. ^e*Para/ortho* = 92:8. ^fUndistinguished 2-/3-substituted regioisomers.

When starting from anisole, the desired product was obtained as a mixture of regioisomers (*para/ortho* = 87:13) probably owing to the relatively high electron-donating ability of methoxy group (Scheme 3, **3l**). The use of acetanilide as the substrate also provided the desired *para*-substituted product in 60% yield, wherein the use of 2 equiv of TfOH was required (Scheme 3, **3m**). Different disubstituted arenes were further tested. When *ortho*-, *meta*-, or *para*-xylene were used, the desired products were exclusively afforded as single regioisomers in high yields (Scheme 3, **3n**, **3o**, and **3p**). When 1,3-dimethoxybenzene reacted with **1a**, the desired product was afforded (*para/ortho* = 92:8) in 90% yield (Scheme 3, **3q**). When *p*-*tert*-butyl-substituted phenol was chosen as the substrate, alkylation occurred at the *ortho*-position of the hydroxy group, yielding **3r** in 70% yield (Scheme 3, **3r**). The use of *p*-methyl-substituted thiophenol as the substrate also afforded the desired product in good yield (Scheme 3, **3s**). Trisubstituted arene was also proven to be applicable to this Friedel–Crafts alkylation with 3-diazoindole, and the use of mesitylene as the arene source gave the desired product in 95% yield (Scheme 3, **3t**). Heteroaromatic thiophene could also be

smoothly alkylated with **1a**, affording the desired products as indistinguishable 2- and 3-substituted regioisomers in a combined yield of 87% (Scheme 3, **3u**).

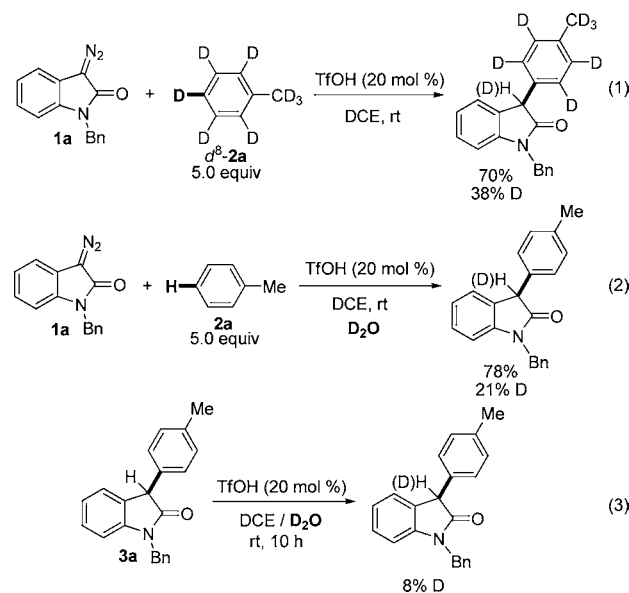
To demonstrate the synthetic practicality of this TfOH-catalyzed aromatic C–H substitution of arene with 3-diazoindole, a gram-scale reaction was carried out by applying 1.50 g of **1a** in toluene. In the presence of 10 mol % of TfOH, this reaction proceeded smoothly at 0 °C to give the desired product **3a** in 75% yield (1.41 g) (Scheme 4).

Scheme 4. Gram-Scale Synthesis of **3a**



In accordance with our previous hypothesis, this aromatic C–H functionalization is proposed to proceed through acid-catalyzed protonation of 3-diazoindole into a diazonium ion followed by Friedel–Crafts alkylation of arenes with concurrent loss of nitrogen (Scheme 2). From detailed kinetic experiments and mechanistic investigations of Brønsted acid-catalyzed hydrolysis of diazocarbonyl compounds,¹¹ it has been shown that the protonation of the diazo carbon atom for the generation of the diazonium ion is the rate-determining step. To gain more insights about this transformation, several deuterium-labeling experiments were conducted. First, *d*₈-substituted toluene was allowed to react with 3-diazoindole **1a** in the presence of 20 mol % of TfOH. The deuterium-substituted product (labeled with 38% deuterium at the C-3 position) was obtained in 70% yield (Scheme 5, eq 1). The low content of deuterium in the product indicated that a direct proton transfer from the aryl ring is unlikely involved. Reaction between **1a** and toluene in D₂O-saturated DCE resulted in the formation of deuterium-substituted product with 21% deuterium in 78% yield (Scheme 5, eq 2). On the other

Scheme 5. Deuterium-Labeling Experiments



hand, stirring **3a** in a mixture of D₂O and DCE for 10 h only resulted in 8% deuterated product, indicating a relatively low rate of H/D exchange of the product (Scheme 5, eq 3). Collectively, these results indicated that small amount of water existed in the mixture may play as a proton shuttle for the acid-catalyzed protonation process.²¹

In summary, we have developed a simple and efficient method for the synthesis of 3-aryloxindoles by TfOH-catalyzed Friedel–Crafts type alkylation of arenes with 3-diazooxindoles. With this metal-free transformation, a series of 3-aryloxindoles were obtained in good yields with high regioselectivities. This reaction is carried out under simple and mild conditions with nitrogen as the only waste and, therefore, shows great potential for application to both laboratory and industrial synthesis.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. 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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- (19) Under the optimal reaction conditions, an array of other types of diazocarbonyl compounds was also evaluated. However, only 3-diazooxindole provided the desired product with satisfactory results in terms of both the yield and regioselectivity (*para* vs *ortho*), indicating the unique reactivity of 3-diazooxindole for this transformation. For details, see Table S1 of the Supporting Information.
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