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Construction of Naphtho-Fused Oxindoles *via* the Aryne Diels–Alder Reaction with Methyleneindolinones

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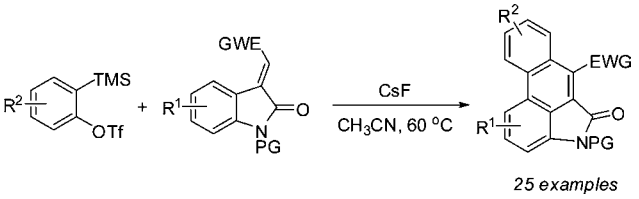
ABSTRACT



Unprecedented aryne Diels–Alder reactions by using methyleneindolinones as dienes have been disclosed, thus providing a quick access to unusual naphtho-fused oxindoles. A wide range of methyleneindolinones proceed readily with arynes to afford the functionalized oxindoles in good yields.

Arynes have proven to be versatile building blocks in organic synthesis because of the inherent high strain created by the formal triple bond.[1] Accordingly, recent decades have witnessed rapid progress in various carbon–carbon and carbon–heteroatom bond-forming reactions using arynes.[2] As such, arynes have been extensively investigated in transition-metal-catalyzed reactions.[3] More recently, much effort has also been focused on transition-metal-free reactions, which mainly involve the addition of nucleophiles to arynes followed by trapping the *in situ* formed anion intermediates with electrophiles.[4] Most importantly, the generation of aryne from *ortho*-(trimethylsilyl)-aryl triflate under mild conditions appears to be the key to the

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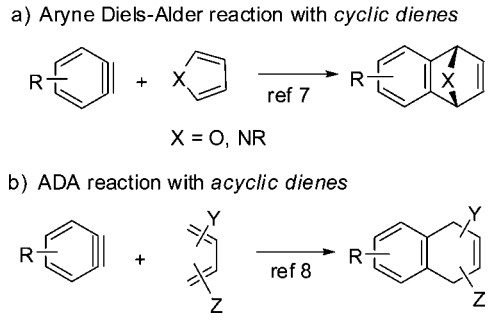
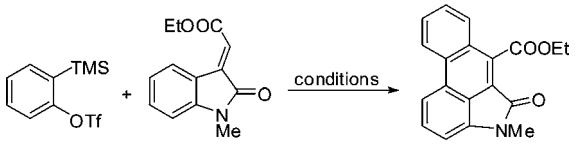
success of these reactions.[5] Owing to their high electrophilicity, arynes can serve as reactive dienophiles in pericyclic reactions.[1b,c] Of note is the aryne Diels–Alder reaction, which has attracted significant attention since its first report by Wittig.[6] Yet, as shown in Scheme 1, whereas cyclic dienes are frequently employed,[7] acyclic dienes are less common.[8]

Scheme 1. Representative Aryne Diels–Alder Reactions



On the other hand, oxindoles are important synthetic targets owing to their significant biological activities including insecticidal, antitumor, anthelmintic, and antibacterial properties.[9] As a result, numerous successful strategies have emerged for the construction of these scaffolds.[10,11] In spite of these considerable advances, however, the application of aryne in oxindole chemistry has not been reported yet. Recently, we have paid much attention to the construction of carbocycles and heterocycles.[12] Thus, several efficient methods for the syntheses of functionalized oxindoles are also disclosed.[12c–e] As a continuation, herein we wish to report the reaction of methyleneindolinones with *in situ* formed arynes, which allows the efficient construction of structurally unusual naphtho-fused oxindoles.

Table 1. Reaction Optimization with Benzyne Precursor **1a** and Oxindolylideneacetate **2a**



1a **2a** **3a**

entry	reagent[a]	solvent	temp (°C)	yield (%)[b]
1	KF	CH_3CN	60	46
2	KF	THF	60	31
3	LiF	CH_3CN	60	trace
4	NaF	CH_3CN	60	trace
5	ZnF_2	CH_3CN	60	trace
6	TBAF	THF	60	–[c]
7	CsF	CH_3CN	60	68
8	CsF	CH_3CN	40	51
9	CsF	CH_3CN	rt	40
10	CsF	THF	60	35
11	CsF	toluene	60	15
12	CsF	DCM	60	trace

[a] 3.0 equiv of the fluoride ion source were employed. [b] Isolated yield of product. [c] A complex mixture was observed.

Our initial experiments began with the investigation of benzyne precursor **1a** and oxindolylideneacetate **2a**. In the presence of KF, cycloadduct **3a** was isolated in 46% yield when CH_3CN was used as solvent (Table 1, entry 1), whereas a lower yield was observed with THF (Table 1, entry 2). However, the replacement of KF with LiF, NaF, or ZnF_2 as a fluoride source only led to the formation of a trace amount of compound **3a** (Table 1, entries 3–5). To our delight, the employment of CsF gave the best results and subsequent experiments also showed that lower temperatures were unfavorable (Table 1, entries 7–9). Finally, the screening of solvents further indicated that the reaction took place most efficiently with CH_3CN as solvent (Table 1, entries 10–12).

With these optimized reaction conditions in hand, we attempted to briefly establish the reaction scope. As shown in Table 2, various substituted oxindolylideneacetates **2** with both electron-withdrawing (Table 2, entries 2–4 and entries 8–10) and -donating substituents (Table 2, entries 5–6 and entry 11) on the aryl ring at position 5, 6, and 7 (Table 2, entry 10) all performed well to produce the cycloadducts **3** in satisfactory yields, and all new compounds were characterized by ^1H, ^{13}C NMR and HRMS spectra.[13] Moreover, the structures of compound **3g** and **3k** (Figure 1) were unambiguously confirmed by single crystal X-ray analysis.[14] Experiments with different protecting groups at the N-atom of **2** were also conducted

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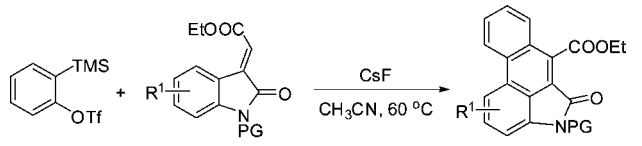
(13) See the Supporting Information for details.

(14) CCDC 887797, CCDC887796 for compounds **3g**, **3k** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Cycloaddition Reaction Using Benzyne Precursor **1a** and Oxindolylideneacetates **2**[a]



1a 2 3

entry	R^1	PG[b]	product	yield (%)[c]
1	H	Me	**3a**	68
2	5-fluoro	Me	**3b**	64
3	5-chloro	Me	**3c**	76
4	6-bromo	Me	**3d**	53
5	5-methyl	Me	**3e**	65
6	5-methoxy	Me	**3f**	70
7	H	Bn[d]	**3g**	77
8	5-chloro	Bn[d]	**3h**	60
9	5-bromo	Bn[d]	**3i**	80
10	7-bromo	Bn[d]	**3j**	75
11	5-methyl	Bn[d]	**3k**	55
12	4-chloro	Me	NR	

[a] The reaction of **1a** (1.0 mmol) and **2** (1.0 mmol) was carried out in the presence of CsF (3.0 equiv) in 10 mL of CH_3CN at 60 °C for 12 h unless otherwise noted. [b] PG = protecting group. [c] Yield of product after silica gel chromatography. [d] Bn = benzyl.

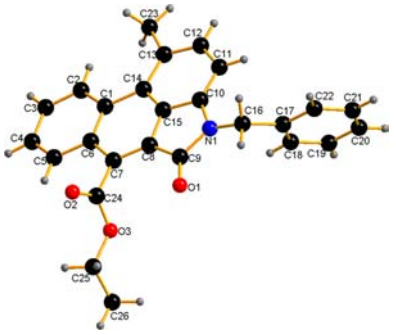
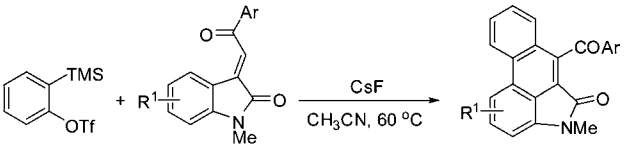


Figure 1. Single crystal X-ray structure for **3k**.

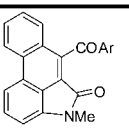
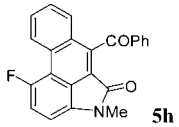
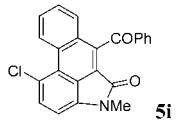
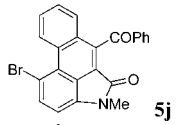
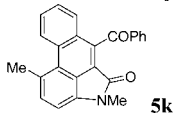
(Table 2, entries 7–11). In such cases, the benzyl group was another good choice. As expected, no reaction occurred when substrate **2** with a substituent at position 4 was used (Table 2, entry 12). Pleasingly, halide and methoxy group substitutions on the aromatic ring were tolerated, which were potentially useful for further functionalization. Most importantly, the present cycloaddition strategy represents an unprecedented example of synthesizing functionalized naphtho-fused oxindoles by using methyleneindolinones as dienes, which provides a convergent and powerful method for the construction of polycyclic skeletons that cannot be otherwise accessed.

To further demonstrate the utility of this annulation procedure, cycloaddition reactions using arenacylideneoxindoles **4** as dienes were also investigated. As shown in

Table 3. Cycloaddition Reaction Using Benzyne Precursor **1a** and Arenacylideneoxindoles **4**[a]



1a 4 5

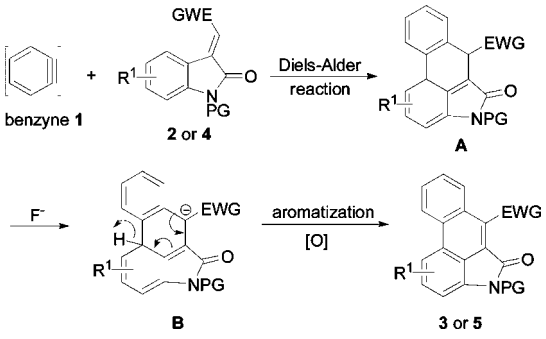
entry	R^1	product		yield (%)[b]
				
1	H	Ar = C_6H_5,	**5a**	58
2	H	Ar = 3-ClC_6H_4,	**5b**	40
3	H	Ar = 4-ClC_6H_4,	**5c**	70
4	H	Ar = 3-MeC_6H_4,	**5d**	46
5	H	Ar = 3-$MeOC_6H_4$,	**5e**	41
6	H	Ar = 4-FC_6H_4,	**5f**	72
7	H	Ar = 4-$NO_2C_6H_4$,	**5g**	67
8	H	Ar = 2-ClC_6H_4		NR
9	5-fluoro		**5h**	51
10	5-chloro		**5i**	62
11	5-bromo		**5j**	71
12	5-methyl		**5k**	75

[a] The reaction of **1a** (1.0 mmol) and **4** (1.0 mmol) was carried out in the presence of CsF (3.0 equiv) in CH_3CN at 60 °C for 8 h unless otherwise noted. [b] Yield of product after silica gel chromatography.

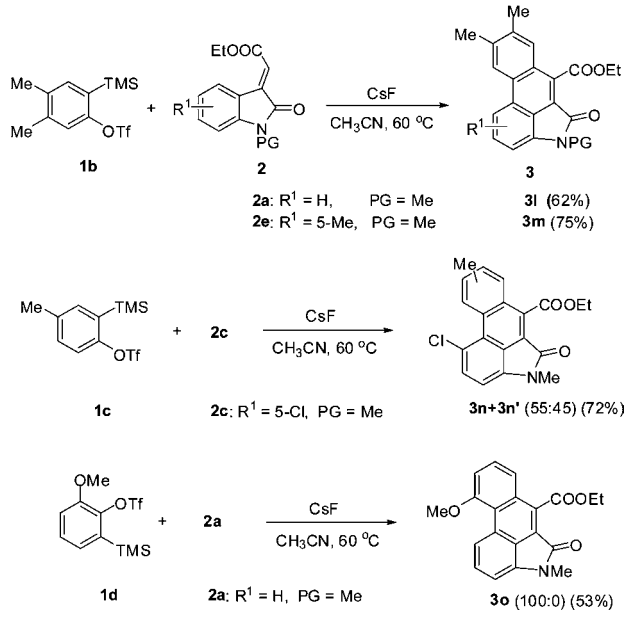
Table 3, changing the substituent at the aromatic ring bearing the carbonyl group of **4** was first carried out (Table 3, entries 2–7). Notably, the presence of substituents at the *meta*-position of substrate **4** usually gave low yields, whereas no formation of **5** was detected when substrate **4** with *ortho*-substitution was used (Table 3, entry 8). In such cases, good yields of products **5** were observed using substrate-containing *para*-substitution. Gratifyingly, substituted arenacylideneoxindoles **4** with electron-deficient and -rich substituents on the oxindole ring proceeded readily under optimal conditions, furnishing the

corresponding cycloadducts **5** in satisfactory yields (Table 3, entries 9–12).

Scheme 2. Proposed Mechanism



Scheme 3. Controlled Experiments with Substituted Arynes **1**



The mechanism of the above cycloaddition reaction has not been unequivocally established, but one reasonable possibility is outlined in Scheme 2. The methyleneindolinone **2** or **4** can act as a diene to react with the *in situ* generated benzyne **1**, affording the [4 + 2] cycloadduct **A**. Subsequently, a fluoride anion also behaves as a base to abstract hydrogen from intermediate **A**, which leads to the formation of anion **B**. Further aromatization yields highly unusual naphtho-fused oxindole **3** or **5**.[8b,c] It is interesting to note that no intermediate **A** or **B** was ever detected in the reaction mixtures,[15] presumably due to the rapid oxidative aromatization following the previous [4 + 2] cycloaddition.

Substituted aryne precursors were next examined (Scheme 3). Reactions of triflate **1b** with oxindolylideneacetate **2** worked well with good yields to afford products **3l** and **3m**. Furthermore, the impact on regioselectivity was also observed when an aryne bearing a substituent was employed. In such a case, regioisomers **3n** and **3n′** were isolated in a ratio of 55:45 (based on ^{1}H NMR). Remarkably, the employment of 3-methoxy substituted triflate **1d** led to excellent regioselectivity. The structure of product **3o** was confirmed by single X-ray analysis.[16]

In conclusion, we have described the cycloaddition reactions of methyleneindolinones and arynes to generate structurally unusual naphtho-fused oxindoles,[17] which are difficult to access by other methods. The present strategy also opens a convergent and powerful pathway for the construction of polycyclic skeletons. Furthermore, this method is also distinguished by its convenient experimental setup and broad substrate scope. A plausible mechanism is proposed to account for the formation of products **3** and **5**, which proceeds through an unusual [4 + 2] cycloaddition followed by isomerization and dehydrogenation processes. Further experiments with a broader substrate scope are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds; crystallographic data in CIF format for **3g** and **3k**. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) See the Supporting Information for details on the controlled experiments. During the investigation, the excessive amount of CsF was also found to play a significant role in the whole transformation.

(16) CCDC900344 for compound **3o** contains the supplementary crystallographic data for this paper.

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The authors declare no competing financial interest.