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A Practical and General Diels–Alder Reaction of Pentafulvenes with Arynes

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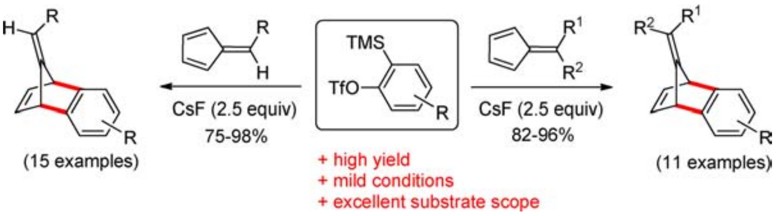
ABSTRACT



+ high yield
+ mild conditions
+ excellent substrate scope

A high-yielding, versatile and practical Diels–Alder reaction of pentafulvenes with arynes under mild reaction conditions is reported. The aryne generated by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates undergoes efficient cycloaddition with 6-substituted and 6,6-disubstituted pentafulvenes leading to the formation of benzonorbornadiene derivatives.

Arynes are highly reactive intermediates that garnered tremendous attention from the chemical community for the construction of multisubstituted arenes of structural diversity and complexity.[1,2] Due to their high electrophilicity, arynes have been shown to react with a wide variety of dienes[3] and dipoles.[4] The Diels–Alder reaction is an important reaction of arynes, which is a powerful tool for constructing various carbocycles and heterocycles of synthetic importance.[3] Among the Diels–Alder reactions of arynes, the reaction of 6,6-dimethylfulvene[5] with aryne generated from 2-bromofluorobenzene leading to the formation of the benzonorbornadiene derivative was reported by Muneyuki and Tanida as early as 1966 (Scheme 1, eq 1).[6] Intriguingly, this reaction is limited to only one fulvene. Subsequently, the reaction of tetrahalogenoarynes generated from pentafluorophenyl lithium with 6,6-dialkylfulvenes was reported by Heaney and co-workers (eq 2).[7] Additionally, the reaction of aryne generated from

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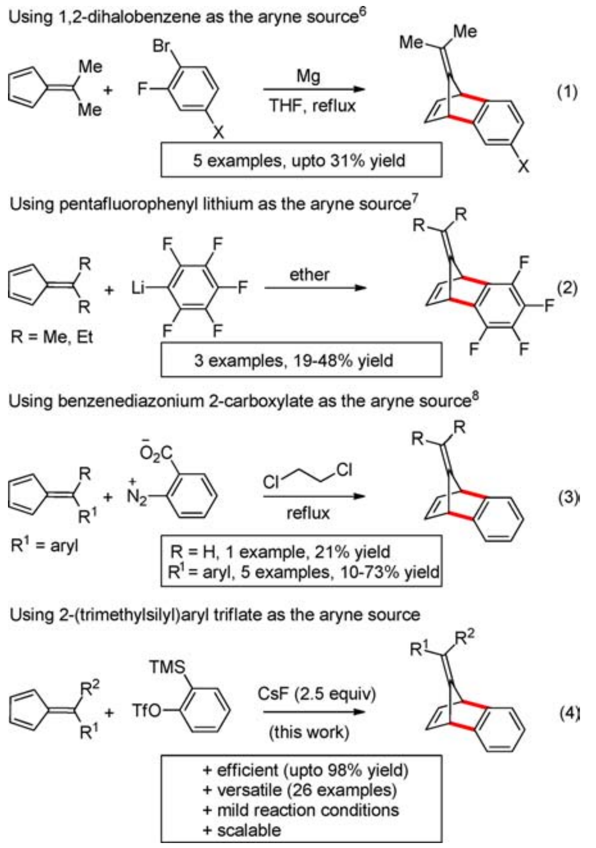
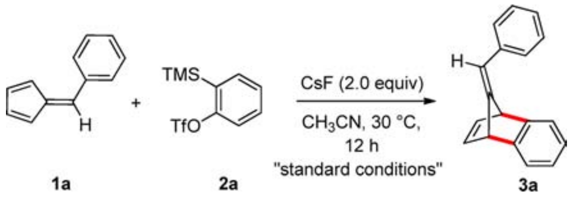
benzenediazonium 2-carboxylate with fulvenes was reported by Adam and co-workers (eq 3).[8] However, in all these reports, the yields are not yet optimal and the substrate scope appears to be very limited, and a general system remains to be uncovered. Herein, we report a high yielding, scalable, and broad substrate scope aryne Diels–Alder reaction with 6-substituted and 6,6-disubstituted pentafulvenes affording benzonorbornadiene derivatives (eq 4). The key to success of the present method is the application of the mild condition for the generation of arynes by the fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates.[9]

Scheme 1. Diels–Alder Reaction of Arynes with Pentafulvenes



We initiated our present study with the treatment of (cyclopenta-2,4-dien-1-ylidenemethyl)benzene **1a** with the aryne generated in situ from 2-(trimethylsilyl)aryl triflate **2a** using 2.0 equiv of CsF. Interestingly, the reaction afforded the benzonorbornadiene derivative **3a** in 94% yield (based on ^{1}H NMR spectroscopy, Table 1, entry 1). It is noteworthy that the reaction worked under mild reaction conditions in CH_3CN as the solvent. The reaction carried out using KF (in the presence of 18-crown-6) as the fluoride source gave similar results, but the use of tetrabutylammonium fluoride (TBAF) was not found to be beneficial (entries 2, 3). Lowering the amount of **1a** or reducing the reaction time lowered the yield of **3a** (entries 4, 5). Finally, increasing the amount of CsF to 2.5 equiv improved the reactivity, with **3a** obtained in 98% yield (entry 6).[10,11]

Table 1. Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions[a]	yield of **3a** (%)[b]
1	none	94
2	KF and 18-crown-6 instead of CsF, THF as the solvent	93
3	TBAF instead of CsF, THF as the solvent	<1
4	1.2 equiv of **1a** instead of 1.5 equiv	87
5	reaction time of 6 h instead of 12 h	80
6	2.5 equiv of CsF instead of 2.0 equiv	>99 (98)

[a] Standard conditions: **2a** (0.25 mmol), **1a** (0.38 mmol), CsF (2.0 equiv), CH_3CN (1.0 mL), 30 °C and 12 h. [b] The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield at 0.50 mmol scale in parentheses.

With the optimized reaction conditions in hand, we then evaluated the substrate scope of this unique fulvene-aryne Diels–Alder reaction (Scheme 2).[12] The unsubstituted parent fulvene derived from benzaldehyde worked well, and a variety of electron-donating and -withdrawing groups at the 4-position of the aromatic ring of **1** were well tolerated, furnishing benzonorbornene derivatives in good to excellent yields (**3a**–**e**). Moreover, substitution is tolerated at the 3- and 2-position of the aromatic ring of **1** resulting in the smooth conversion to the product (**3f**, **3g**). Additionally, the fulvene derived from 1-naphthaldehyde and 3,4-dimethoxy benzaldehyde worked well to afford the product in excellent yield (**3h**, **3i**). Gratifyingly, fulvenes derived from challenging aldehydes like ferrocene carboxaldehyde and a heterocyclic aldehyde also resulted in the formation of the desired product further expanding the scope of this aryne Diels–Alder reaction (**3j**, **3k**). Furthermore, the reaction is not just limited to fulvenes derived from aromatic aldehydes. Delightfully, fulvenes derived from aliphatic aldehydes also worked well leading to the

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(8) (a) Adam, W.; Lucchini, V.; Peters, E.-M.; Peters, K.; Pasquato, L.; Georg von Schnering, H.; Seguchid, K.; Waltera, H.; Will, B. *Chem. Ber*. **1989**, *122*, 133. Notably in this report, a single example of the aryne cycloaddtion with benzaldehyde-derived pentafulvene in 21% yield was presented. See also: (b) Paquette, L. A.; Kukla, M. J.; Stowell, J. C. *J. Am. Chem. Soc*. **1972**, *94*, 4920. (c) Warrener, R. N.; Collin, G. J.; Foley, P. J. *Molecules* **2001**, *6*, 194.

(9) (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett*. **1983**, 1211. For a modified procedure, see: (b) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454.

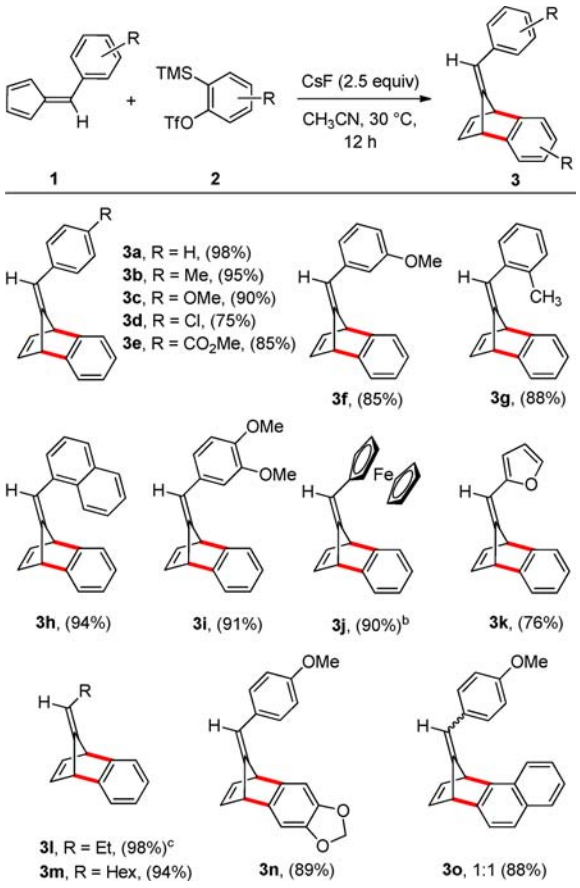
(10) The same yield was obtained from a 2.0 mmol scale reaction.

(11) For details, see the Supporting Information.

(12) In view of the lower stability of the fulvenes, we used freshly prepared fulvenes for all the reactions in Scheme 2.

desired products in excellent yields (**3l**, **3m**). Finally, the versatility of the present reaction was examined using substituted aryne precursors. A symmetric aryne having a heteroatom substituent generated from **2n** underwent efficient cycloaddition with fulvene leading to the formation of the cycloadduct **3n** in 89% yield. Interestingly, an unsymmetric aryne generated from 1-(trimethylsilyl)-2-naphthyltriflate furnished a diastereomeric mixture of a cycloadduct in a 1:1 ratio and an 88% yield (**3o**).

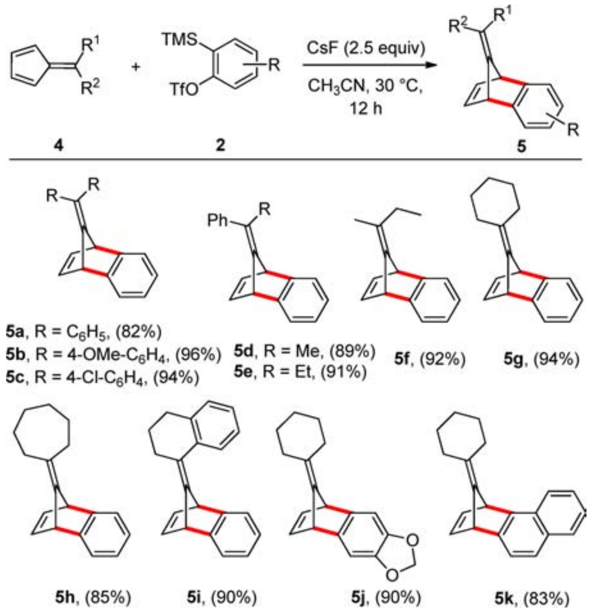
Scheme 2. Diels–Alder Reaction of Arynes with 6-Substituted Pentafulvenes[a]



[a] General conditions: **2** (0.50 mmol), **1** (0.75 mmol), CsF (2.5 equiv), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given. [b] Reaction run on 0.2 mmol scale. [c] The reaction run using 2.0 equiv of fulvene **1l**.

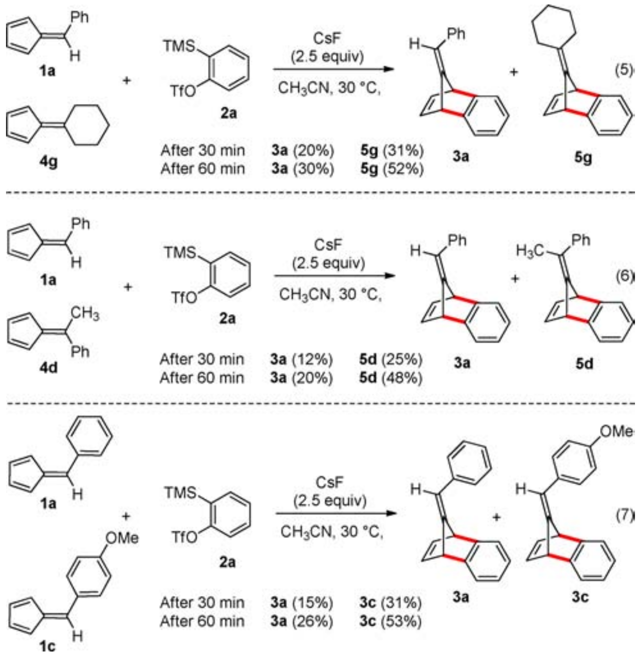
After examining the Diels–Alder reaction of arynes with aldehyde-derived fulvenes, we focused our attention on 6,6-disubstituted fulvenes **4** (Scheme 3), which are easily prepared by the condensation of cyclopentadiene and the corresponding ketones.[13] Fulvenes derived from electronically different benzophenones afforded the cycloadduct **5a–c** in 82–96% yield, and fulvenes synthesized from alkyl aryl ketones resulted in the smooth conversion to the bicyclic product in excellent yield (**5d**, **5e**). Gratifyingly, fulvenes derived from acyclic and cyclic ketones are tolerated well (**5f–i**) with isolated yields above 85% in each case demonstrating the versatility of the present reaction. Moreover, symmetric and unsymmetric substituted arynes

Scheme 3. Diels–Alder Reaction of Arynes with 6,6-Disubstituted Pentafulvenes[a]



[a] General conditions: **2** (0.50 mmol), **4** (0.75 mmol), CsF (2.5 equiv), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given.

Scheme 4. Intermolecular Competition Experiments[a]



[a] The yields were determined by ^1H NMR analysis of crude products using CH_2Br_2 as the internal standard.

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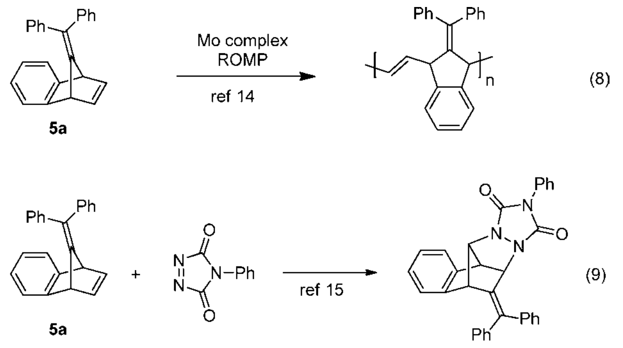
Scheme 5. Synthetic Utility of the Cycloadducts



also afforded good to excellent yield of the cycloadduct (**5j**, **5k**) significantly expanding the scope of this reaction.

Further experiments shed light on the reactivity of 6-substituted and 6,6-disubstituted pentafulvenes toward arynes. Intermolecular competition experiments carried out using electronically and sterically different pentafulvenes **1a** and **4g** revealed that the 6,6-dialkyl substituted fulvene **4g** reacted ∼1.6 times faster than the 6-aryl fulvene **1a** (Scheme 4, eq 5).[11] This indicates that the dialkyl substitution at the 6-position makes the diene system in **4g** more electron-rich, thus facilitating an efficient Diels−Alder reaction. Hence, it is reasonable to assume that the electronic nature of the fulvenes is more prominent than the steric factor in the aryne Diels−Alder reaction with pentafulvenes. Similarly, intermolecular competition experiments carried out using pentafulvenes **1a** and **4d** showed that the 6,6-alkylaryl substituted fulvene **4d** reacted ∼2.0 times faster than the 6-aryl fulvene **1a** (eq 6). Interestingly, competition experiments carried out using electronically different 6-substituted pentafulvenes **1a** and **1c** revealed that the electron-rich fulvene **1c** reacted ∼2.0 times faster than the electron neutral one (eq 7).[11]

The benzonorbornadienes **3** and **5** have potential applications in organic chemistry. Ring-opening metathesis polymerization (ROMP) of **5a** using Mo carbene initiators afforded highly stereoregular polymers.[14] (Scheme 5, eq 8) In addition, the addition of **5a** to 4-phenyl-4*H*-1,2,4-triazole-3,5-dione (PTAD) resulted in a convenient entry to polycyclic azoalkanes, which are valuable target molecules (eq 9).[8,15,16]

In conclusion, we have developed a practical, scalable, and efficient Diels−Alder reaction of pentafulvenes with arynes leading to benzonorbornadiene derivatives. Broad substrate scope, high yields, and mild reaction conditions are the noteworthy features of the present reaction. Further studies on the Diels−Alder reaction of arynes with challenging dienes and the application of arynes in various carbon−carbon bond-forming reactions are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.