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# Novel Silver Tetrafluoroborate Catalyzed Electrophilic Cascade Cyclization Reaction: A Facile Approach to the Synthesis of Halo-Substituted Benzo[*a*]fluorenols

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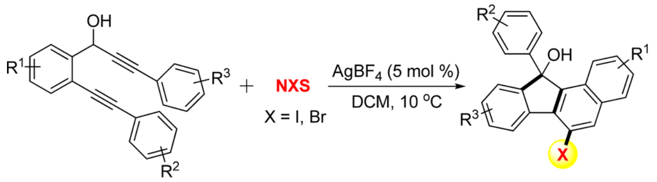
## ABSTRACT



**A facile and novel silver tetrafluoroborate catalyzed electrophilic cascade cyclization reaction to generate halo-substituted benzo[*a*]fluorenols under mild conditions is disclosed. Good chemical selectivity and mild reaction conditions were involved in the transformation. The halide-containing benzo[*a*]fluorenols could be further elaborated via palladium-catalyzed cross-coupling reactions to introduce complexity.**

Transition-metal-catalyzed or electrophile-promoted carbocyclization reactions with tethered alkynes have proven to be powerful methods for the selective generation of functionalized cyclic compounds that are generally not easily accessible via classical pericyclic reactions.[1,2] However, there are only limited reports concerning the combination of a transition metal and an electrophile to produce complex carbocyclic ring systems in a cascade fashions in the literature.[3] Transition-metal-catalyzed electrophilic cascade cyclization reactions show undeniable benefits, such as good chemo- or regioselectivity, mild conditions, as well as high economical and ecological merits.

On the other hand, it is well-known that fused fluorene derivatives are widely applied in optoelectronic materials or devices because of their highly conjugated rigid systems.[4] In addition, they have been widely found in numerous natural products that exhibit interesting biological activities.[5] For instance, kinamycin D,[5a] which was produced by *Streptomyces murayamaensis* and recognized as 5-diazobenzo[*b*]fluorene, is a naturally occurring diazo

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[1] For selected reviews on transition-metal-catalyzed cyclizations, see: (a) Larock, R.; In Acetylene Chemistry. *Chemistry, Biology, and Material Science*; Diederich, F., Stang, P., Tykwinski, R., Eds.; Wiley-VCH: New York, 2005; Chapter 2, pp 51−99. (b) Nicolaou, K.; Edmonds, D.; Bulger, P. *Angew. Chem.* **2006**, *118*, 7292. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Michelet, V.; Toullec, P. Y.; Genêt, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (d) Yu, Z.; Wang, Y.; Wang, Y. *Chem. Asian J.* **2010**, *5*, 1072. (e) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954.

[2] For selected reviews on electrophilic cyclization, see: (a) Rodríguez, F.; Fananas, F. J. In *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley-VCH: New York, 2010; Vol. 2, p 951. (b) Godoi, B.; Schumacher, R.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.

[3] For a Brønsted acid promoted electrophilic cascade cyclization to generate heterocyclic compounds, see:Ali, S.; Li, Y.; Anwar, S.; Yang, F.; Chen, Z.; Liang, Y. *J. Org. Chem.* **2012**, *77*, 424.

[4] (a) Shimizu, A.; Tobe, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 6906. (b) Liu, T.; Xing, C.; Hu, Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 2909. (c) Allard, S.; Forster, M.; Souharce, B.; Thiem, H.; Scherf, U. *Angew. Chem., Int. Ed.* **2008**, *47*, 4070.

[5] (a) Gould, S.; Melville, C.; Cone, M.; Chen, J.; Carney, J. *J. Org. Chem.* **1997**, *62*, 320. (b) Gould, S.; Tamayo, N.; Melville, C. R.; Cone, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 2207. (c) Mithani, S.; Weeratunga, G.; Taylor, N. J.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1994**, *116*, 2209. (d) Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1973**, *21*, 931. (e) Furusaki, A.; Matsui, M.; Watanabe, T.; Omura, S.; Nakagawa, A.; Hata, T. *Isr. J. Chem.* **1972**, *10*, 173. (f) Gould, S.; Melville, C. *Bioorg. Med. Chem. Lett.* **1995**, *6*, 51.

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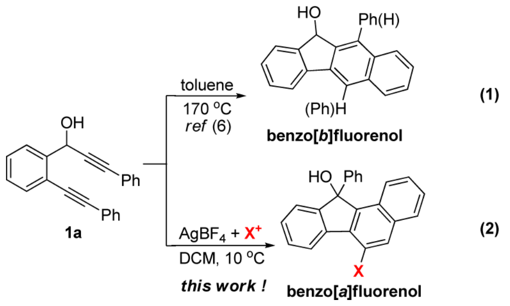
compound that possesses modest antitumor properties and antibiotic activity against Gram-positive organisms.[5b,c] The kinobscurinone, benzo[*b*]fluorenone, was recently shown to be a more advanced intermediate in kinamycin biosynthesis.[5f] Thus, there has been increased interest in the synthesis of the fused benzofluorenes. Recently, Saá and co-workers reported the thermal cycloaromatization of aryldiacetylenes such as nonconjugated benzotriynes and benzodiynes to produce benzo[*b*]fluorene and benzo[*c*]fluorene skeletons (Scheme 1, eq 1).[6] In 2009, Zhang reported a four-example reaction of gold-catalyzed tandem reactions to afford benzo[*a*]fluorenols in moderate to good yields.[7] These achievements, however, often suffered from harsh reaction conditions, tedious separation procedures of the isomers, or limited examples.

In the context of our ongoing interest in transition-metal-catalyzed tandem reactions,[8] as well as our efforts to develop efficient methodologies in electrophilic cyclization reactions,[9] we envisioned that under a suitable Lewis acid catalyst the 1,6-diyn-4-en-3-ols **1a** might react with an electrophile to give a fused benzofluorene under environmentally benign conditions. Herein, we disclose the first transition-metal-catalyzed electrophilic cascade cyclization reaction of benzodiyne **1** with an halogen-containing electrophile, which affords the unexpected halo-containing benzo[*a*]fluorenols **2** at room temperature in moderate to good yields (Scheme 1, eq 2).[10] The obtained halogen-containing benzo[a]fluorenols could be decorated to more complex products via palladium-catalyzed cross-coupling reactions.

**Scheme 1.** Research Design



Initial investigations using 1,6-diyn-4-en-3-ols **1a** and an electrophile, *N*-iodosuccinimide (NIS), as substrates were aimed at determining the reaction outcomes and optimizing the reaction conditions.[11] Unfortunately, no reaction was occurred in the presence of 1.0 equiv of $FeCl_3$ or a catalytic amount of $FeCl_3 \cdot 6H_2O$ or CuI as indicated by crude NMR analysis. However, to our delight, when the starting materials were treated with 10 mol % of $Cu(OTf)_2$ under $N_2$, a product was isolated in 36% yield, which was identified as the iodo-substituted benzo[*a*]fluorenol **2a**. The structure of **2a** was verified by X-ray diffraction analysis (see the Supporting Information). No reaction occurred when a hard Lewis acid, such as $In(OTf)_3$ or $NiCl_2(PPh_3)_2$, was employed as the catalyst in the reaction. Further screening of the catalysts demonstrated that AgOTf was a choice for this transformation, while a cocatalyst system of $PPh_3AuCl$ and AgOTf was examined to be less reactive. Moreover, the significance of silver salts as catalysts revealed that $AgBF_4$ was shown to be the best catalyst as compared with the other silver salts such as $Ag_2CO_3$, AgF, $AgNO_3$, and $AgSbF_6$, and the yield could be improved to 76% when the reaction was performed in dichloromethane.

Surprisingly, the Lewis acid catalyst was found to be crucial for the transformation. Brønsted acids, such as $TsOH \cdot H_2O$ and $CF_3COOH$, or in the absence of a catalyst were proved to be inert for the product generation.[11] No improvements of the yield were observed when water or 4 Å MS as well as an inorganic base were added as additives into the reaction. The amount of catalyst was examined as well. On decreasing the catalyst loading to 2 mol %, the reaction time was prolonged but the yield was decreased dramatically (32% yield). Further evaluation of the solvent effects revealed that dichloromethane (DCM) was the solvent of choice, and other organic solvents such as $CHCl_3$, $CH_3CN$, MeOH, toluene, or THF did not facilitate the formation of **2a**. Elevating the reaction temperature to 30 °C could slightly shorten the reaction time to about 10 h but resulted in a lower yield.

As for the electrophilic reagent screening, we were pleased to find that the *N*-bromosuccinimide (NBS) worked as an electrophile and could also be involved in the transformation. For the reaction of *N*-chlorosuccinimide (NCS) with 1,6-diyn-4-en-3-ols **1**, the starting materials could also be consumed, but the reaction became complex and some unidentified compounds were isolated. In addition, we found that in the presence of 2.5 equiv of

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(6) (a) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **1999**, *40*, 7701. (b) Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2000**, *2*, 1497. (c) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **2002**, *43*, 2717. (d) Rodríguez, D.; Quintás, D.; García, A.; Saá, C; Domínguez, D. *Tetrahedron Lett.* **2004**, *45*, 4711.

(7) (a) Liu, L.; Zhang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6093. (b) Liu, L.; Wei, L.; Zhang, J. *Adv. Synth. Catal.* **2010**, *352*, 1920.

(8) (a) Chen, Z.; Gao, L.; Ye, S.; Ding, Q.; Wu, J. *Chem. Commun.* **2012**, *48*, 3975. (b) Gao, L.; Ye, S.; Ding, Q.; Chen, Z.; Wu, J. *Tetrahedron* **2012**, *68*, 2765. (c) Ye, C.; Chen, Z.; Wang, H.; Wu, J. *Tetrahedron* **2012**, *68*, 5197. (d) Chen, Z.; Ye, C.; Gao, L.; Wu, J. *Chem. Commun.* **2011**, *47*, 5623. (e) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (f) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856. (g) Chen, Z.; Yu, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 6356. (h) Yu, X.; Chen, Z.; Yang, X.; Wu, J. *J. Comb. Chem.* **2010**, *12*, 374. (i) Chen, Z.; Yang, X.; Wu, J. *Chem. Commun.* **2009**, 3469.

(9) (a) Chen, Z.; Ding, Q.; Yu, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 1692. (b) Chen, Z.; Yu, X.; Su, M.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702. (c) Chen, Z.; Su, M.; Yu, X.; Wu, J. *Org. Biomol. Chem.* **2009**, *7*, 4641. (d) Chen, Z.; Pan, X.; Wu, J. *Synlett* **2011**, 964. (e) Ding, Q.; Chen, Z.; Yu, X.; Peng, Y.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 340.

(10) For a recent iodocyclization reaction of 1,6-diyn-4-en-3-ols **1** with ICl to produce 1,3-diiodinated naphthalene derivatives, see: (a) Wang, L.; Zhu, H.; Lu, L.; Yang, F.; Liu, X.; Liang, Y. *Org. Lett.* **2012**, *14*, 1990. For recent examples on gold-catalyzed cyclizations of benzodiyne **1**, see: (b) Chen, Y.; Chen, M.; Liu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 6181. (c) Chen, Y.; Chen, M.; Liu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 6493.

(11) For details, see the Supporting Information.

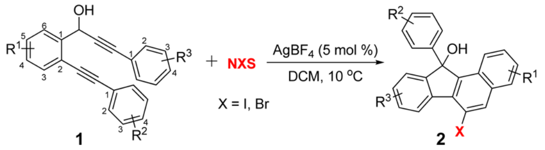
(12) (a) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259. (b) Shi, M.; Horn, M.; Kobashiya, S.; Mayr, H. *Chem.—Eur. J.* **2009**, *15*, 8533.

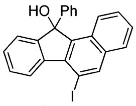
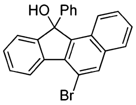
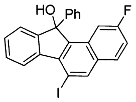
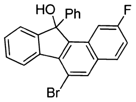
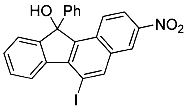
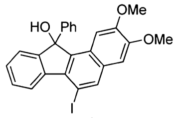
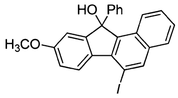
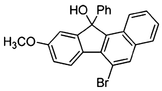
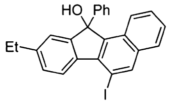
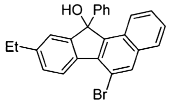
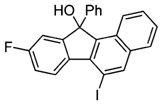
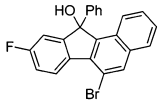
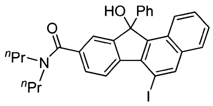
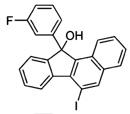
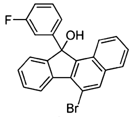
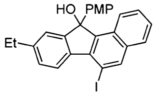
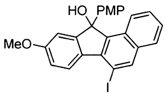
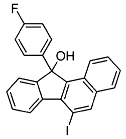
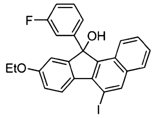
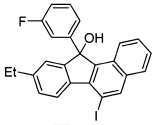
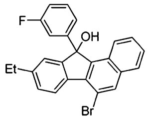
(13) (a) Kitamura, T.; Kobayashi, S.; Taniguchi, H.; Rappoport, Z. *J. Org. Chem.* **1982**, *47*, 5003. (b) Chen, X.; Lu, P.; Wang, Y. *Chem.—Eur. J.* **2011**, *17*, 8105.

$NaHCO_3$, electrophiles such as iodine, bromine, or ICl could also be reactive under the $AgBF_4$-catalyzed electrophilic cascade cyclization reactions. Although all of the iodine-, bromine-, or ICl-mediated tandem electrophlic cyclizations generally have lower yields than those of the corresponding outcomes when using NIS or NBS as substrates, these reactions, however, could also serve as an alternative method for the generation of halo-substituted benzo[*a*]fluorenols. For details, see the Supporting Information.

With the optimized conditions [$AgBF_4$ (5 mol %), DCM, 10 °C] in hand, we next explored the generality of the reaction, and the results are summarized in Table 1. For all cases, 1,6-diyn-4-en-3-ols **1** reacted with NXS (X = I, Br) leading to the corresponding iodo- or bromo-substituted benzo[*a*]fluorenols **2** in moderate to good yields.

**Table 1.** Sequential Electrophilic Cyclization Reaction to Halogen-Substituted Benzo[*a*]fluorene Derivatives



| entry | $R^1$, $R^2$, $R^3$ (**1**) | NXS | product (**2**) | yield (%)[a] |
|---|---|---|---|---|
| 1 | H, H, H (**1a**) | NIS |  | 76 (**2a**) |
| 2 | (**1a**) | NBS |  | 60 (**2b**) |
| 3 | 4-F, H, H (**1b**) | NIS |  | 63 (**2c**) |
| 4 | (**1b**) | NBS |  | 61 (**2d**) |
| 5 | 5-$NO_2$, H, H (**1c**) | NIS |  | 78 (**2e**) |
| 6 | 4,5-diMeO, H, H (**1d**) | NIS |  | complex |
| 7 | H, H, 4-MeO (**1e**) | NIS |  | 70 (**2f**) |
| 8 | (**1e**) | NBS |  | 69 (**2g**) |
| 9 | H, H, 4-Et (**1f**) | NIS |  | 57 (**2h**) |
| 10 | (**1f**) | NBS |  | 45 (**2i**) |
| 11 | H, H, 4-F(**1g**) | NIS |  | 45 (**2j**) |
| 12 | (**1g**) | NBS |  | 50 (**2k**) |
| 13 | H, H, 4-CON$^n$$Pr_2$ (**1h**) | NIS |  | 35 (**2l**) |
| 14 | H, 3-F, H (**1i**) | NIS |  | 42 (**2m**) |
| 15 | (**1i**) | NBS |  | 43 (**2n**) |
| 16 | H, 4-MeO, 4-Et (**1j**) | NIS |  | 35 (**2o**)[b] |
| 17 | H, 4-MeO, 4-MeO (**1k**) | NIS |  | complex |
| 18 | H, 4-F, H (**1l**) | NIS |  | 53 (**2p**) |
| 19 | H, 3-F, 4-EtO (**1m**) | NIS |  | 47 (**2q**) |
| 20 | H, 3-F, 4-Et (**1n**) | NIS |  | 46 (**2r**) |
| 21 | (**1n**) | NBS |  | 52 (**2s**) |

[a] Isolated yield based on 1,6-diyn-4-en-3-ols **1**. [b] PMP = 4-MeO-Ph.

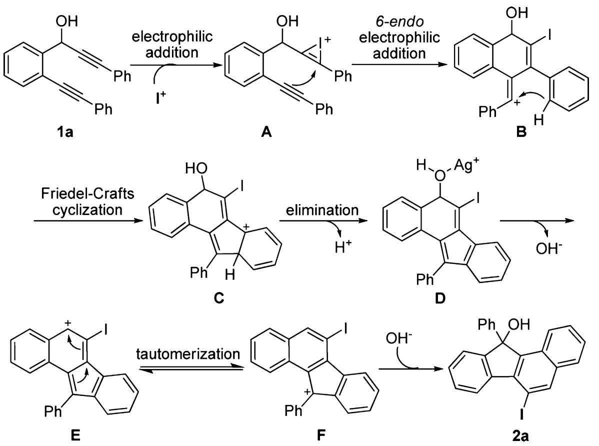
For example, good results were obtained when an electron-withdrawing group was linked on the R$^1$ position; the 4-F substituted compound **1b** reacted with NIS or NBS gave the corresponding iodo- or bromo-substituted benzo[*a*]fluorenols **2c** or **2d** in 63% or 61% yield, respectively (Table 1, entries 3 and 4). The structure of **2c** was confirmed by X-ray diffraction analysis as well (Supporting Information). A good result (**2e**, 78% yield) was obtained when 5-$NO_2$ was attached on the R$^1$ ring (Table 1, entry 5). The reaction got complex when two electron-donating group substituted compound **1d** was involved in the reaction, which might be because the two electron-rich triple bonds became too reactive for the silver-catalyzed electrophilic cascade cyclization reaction, thus leading less chemoselectivity under the reaction conditions (Table 1, entry 6).

Good yields were observed when electron-donating groups such as MeO- or Et- were linked on the R$^3$ position (Table 1, entries 7–10). While for the F-substitued starting material **1g** reacted with NIS and NBS, the corresponding halo-substitued benzo[*a*]fluorenols **2j** and **2k** could be isolated in 45% and 50% yield, respectively (Table 1, entries 11 and 12). However, an inferior yield was displayed when 4-CON($^n$Pr)$_2$-substituted benzodiyne **1h** was employed in the reaction (35% yield, Table 1, entry 13). The reaction was complex when 4-$NH_2$- or 4-N(Boc)$_2$-substituted benzodiyne was employed, and an unknown molecular could be isolated from the reaction of 4-COOMe-substituted benzodiyne with NIS (data not shown in Table 1).

For various substituents attached on the R$^2$ aromatic ring, it could be noticed from Table 1 that generally moderate yields were obtained whether electron-donating or -withdrawing groups were attached. For example, the R$^2$ = 3-F-substituted benzodiyne **1i** reacted with NIS and NBS to give the corresponding products **2m** and **2n** in 42% and 43% yield, respectively (Table 1, entries 14 and 15). For the reaction of substrate **1j** (R$^2$ = 4-MeO) with NIS, the desired benzo[*a*]fluorenol product **2m** could be formed in 35% yield under the standard conditions (Table 1, entry 16), whereas a complex reaction was observed for the substrate **1k** substituted with two strong electron-donating groups (Table 1, entry 17). For further examination of other R$^2$ = 4-F- or 3-F-substituted substrates **1l**–**n**, the reactions also proceeded smoothly to give the desired products in moderate yields (Table 1, entries 18–21).

On the basis of the above observations, we proposed a plausible mechanism for the silver tetrafluoroborate catalyzed electrophilic cascade cyclization reaction (Scheme 2). We envisioned that in the presence of a Lewis acid catalyst one of the triple bonds was easily converted to iodonium intermediate **A**, which could be electrophilically attacked by the other triple bond through an intramolecular *6-endo* cyclization to produce a vinylic carbocation **B**.[12] Subsequently, intramolecular Friedel–Crafts cyclization occurred, and then the proton was released to produce an intermediate **D**.[13] Finally, the hydroxy group, which could be activated by the Lewis acid, would be released and the positive ion intermediate **E** would undergo an intramolecular tautomerization to produce the tertiary carbonium **F**, and **2a** was produced.

**Scheme 2.** Plausible Mechanism for the Silver Tetrafluoroborate Catalyzed Sequential Electrophilic Cyclization Reaction



As mentioned above, the halo-substituted benzo[*a*]fluorenols **2** could be easily elaborated via known palladium-catalyzed cross-coupling reactions.[9a,c] Thus, the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of compound **2a** with 4-methylphenylboronic acid in DMF–$H_2O$ at 50 °C proceeded smoothly to give the corresponding product **3a** in a quantitative yield. In the Sonogashira coupling reaction, compound **2a** reacted with 4-methylphenylacetylene to give rise to the desired product **4a** in 83% yield.

In summary, we have described a novel silver tetrafluoroborate catalyzed electrophilic cascade cyclization reaction of benzodiyne with electrophiles for the construction of halo-substituted benzo[*a*]fluorenols, which could be further elaborated via palladium-catalyzed cross-coupling reactions to introduce complexity. The reaction features high chemoselectivity and mild reaction conditions toward the starting benzodiynes, introducing the possibility of preparing a tetracyclic nucleus scaffold from which a library of optoelectronically or biologically interesting compounds could be constructed. More detailed mechanistic studies and further application of this chemistry are underway in our laboratory.

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**Supporting Information Available.** Experimental procedure, characterization data, $^1$H and $^{13}$C NMR spectra of compounds **2**, and X-ray data for compounds **2a** and **2c** (CIF). 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.