# Iron-Catalyzed Cascade Arene−Aldehyde Addition/Cyclizations for the Highly Efficient Synthesis of Xanthenes and Its Analogous: Observation of a C−C Bond Cleavage in Indole-Based Triarylmethanes

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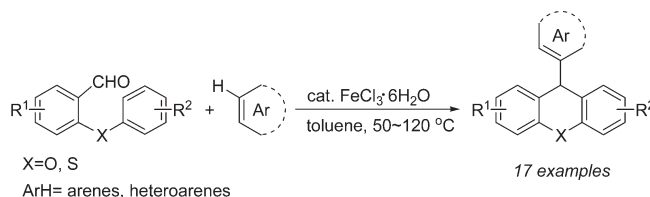
An efficient, general, and one-pot procedure for the synthesis of multisubstituted xanthene derivatives through Fe(III)-catalyzed reactions of 2-aryloxybenzaldehydes with electron-rich arenes has been developed. This method offers several advantages such as high selectivities, mild reaction conditions, and easily accessible starting materials. A mechanistic study revealed that a C−C bond cleavage of a triarylmethane intermediate might be involved in the domino process.

Introduction

The development of sustainable, environmentally benign C−C bond-forming processes is one of the fundamental goals in organic chemistry. As a result, iron-catalyzed reactions have received considerable attention due to the unique properties of iron and its complexes, such as having a low price and being nontoxic and easy to synthesize.[1] On the other hand, transition metal- or Lewis acid-catalyzed direct functionalization of aromatic C−H bonds to form C−C bonds has emerged as a rapid and efficient access to a variety of arenes and heteroarenes, which are highly useful synthetic intermediates in the fields of organic and organometallic chemistry.[2] In this regard, Lewis acid-catalyzed addition of electron-rich arenes to aldehydes or imines via a double Friedel−Crafts process represents a valuable and atom economic protocol for the construction of triarylmethanes.[3] Various catalytic systems such as $AuCl_3$,[3a] $Cu(OTf)_2$,[3b,c] $Sc(OTf)_3$,[3b] [Ir(COD)Cl]$_2$−$SnCl_4$,[3d] and $FeCl_3$[3e−g] are able to catalyze these types of reactions under mild reaction conditions. Meanwhile, the synthesis of unsymmetrical

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TABLE 1. Optimization Studies for the Metal-Catalyzed Xanthene Formation Reactions
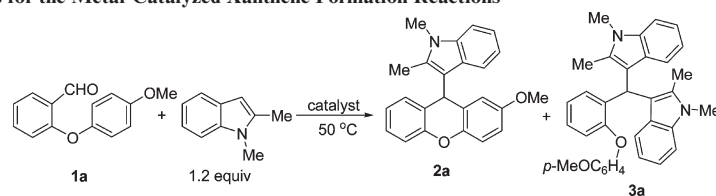
entry	catalyst	solvent	time	yield (%) of 2a[a]	yield (%) of 3a[a]
1	5 mol % of AuCl$_3$	toluene	3 h	25	32
2	10 mol % of FeCl$_3 \cdot$6H$_2$O	toluene	3 h	84	
3	10 mol % of FeCl$_3 \cdot$6H$_2$O	DCE	5 h	72	
4	10 mol % of FeCl$_3$	toluene	3 h	74	
5		toluene	12 h	NR[b]	
6	20 mol % of BF$_3 \cdot$Et$_2$O	toluene	2 h	72	
7	20 mol % of BF$_3 \cdot$Et$_2$O	DCE	1 h	73	
8	5 mol % of AgOTf	toluene	14 h	51	
9	10 mol % of ZnCl$_2$	toluene	12 h	40	36
10	10 mol % of TfOH	toluene	1 h	79	
11	5 mol % of TfOH	toluene	1 h	84	
12	10 mol % of TsOH·H$_2$O	toluene	1 h	75	
13	5 mol % of TsOH·H$_2$O	toluene	1.5 h	77	
14	10 mol % of HCl[c]	toluene	6 h		49[d]

[a] Isolated yields. [b] NR is no reaction. [c] HCl was used as a 3.08 M solution in Et$_2$O. [d] 32% 1a was recovered.

SCHEME 1
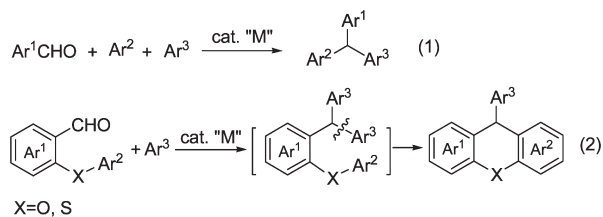
triarylmethanes with three different arenes has also been developed[3b,g,4] (Scheme 1, eq 1). Generally, the literature reports concentrated on the intermolecular reactions to generate noncyclized triarylmethanes; there are rare reports for the construction of cyclic derivatives by these attractive methodologies. During our ongoing research program on acid-catalyzed Friedel−Crafts reactions for the synthesis of polycyclic aromatic compounds under extreme mild conditions,[5] we found that iron salts could catalyze a new domino process of inter- and intramolecular Friedel−Crafts alkylation of arenes. In this paper, we report a highly efficient approach for the synthesis of functionalized xanthenes through iron-catalyzed annulation of arenes with 2-aryloxybenzaldehydes; we would like also to describe our discovery and investigation of a novel C−C bond cleavage in the indole-based triaylmethane intermediates (Scheme 1, eq 2). It is notable that

iron-catalyzed C−C bond cleavage reactions are quite rare,[6] and there are also no reports by applying the Fe-catalyzed C−C bond cleavage reaction for the construction of valuable cyclic compounds, to the best of our knowledge.

Results and Discussion

The substrates of 2-aryloxybenzaldehydes **1** were easily prepared through nucleophilic aromatic substitution of 2-fluorobenzaldehydes with phenols.[7] We initiated our studies by reacting 2-(4-methoxyphenoxy)benzaldehyde **1a** with 1,2-dimethyl-1*H*-indole in the presence of 5 mol % of AuCl$_3$ in toluene at 50 °C (Table 1, entry 1). It was found that the desired 9-indolylxanthene **2a** was formed in 25% yield after 3 h, along with 32% yield of 1-aryl-1,1-bis(1*H*-indol-3-yl)methane **3a**. Advantageously, the use of FeCl$_3 \cdot$6H$_2$O[8] afforded the xanthene **2a** in 84% yield (entry 2). Monitoring the reaction process by TLC revealed that the bis(1*H*-indol-3-yl)methane **3a** was also formed as an intermediate; however, it could be completely consumed after 3 h. Changing the solvent to DCE also afforded 72% yield of **2a** with a longer reaction time (5 h, entry 3). When FeCl$_3$ was used as catalyst, the desired product **2a** was formed in 74% yield (entry 4). Without any catalyst, no reaction occurred (entry 5), suggesting that these results correspond to a iron-catalyzed double alkylation process. Further studies revealed that BF$_3 \cdot$Et$_2$O was also a good catalyst for inducing cyclization reactions, although a higher catalyst loading of 20% was needed to achieve the better yield (entries 6 and 7). Other Lewis acids such as AgOTf and ZnCl$_2$ showed morderate activity for this reaction (entries 8 and 9). Brønsted acids such as TfOH and TsOH·H$_2$O also catalyze the reaction, in which the products were formed in 75−84% yields (entries 10−13). The structure

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TABLE 2. Iron-Catalyzed Domino Process to Substituted Xanthenes

entry	ArCHO	Ar-H	product	yield(%)[a]
1	1a		2b	87
2	1b		2c	82
3	1c		2d	79
4	1e		2e	94
5	1f		2f	76[b]
6	1a		2g	73
7	1a		2h	61[c]

Ar= 2-methyl-1*H*-indol-3-yl

[a] Isolated yield. Unless noted, all the reactions were carried out at 50 °C for 1 h with 10 mol % of FeCl$_3$·6H$_2$O as catalyst and 1.2 equiv of arenes in toluene. [b] 50 °C, 4 h. [c] 2.0 equiv of indole and 50 mol % of FeCl$_3$·6H$_2$O were used, and the reaction temperature was 100 °C.

SCHEME 2

$$3a \xrightarrow[\text{toluene, 50°C, 2.5 h}]{10\% \text{ FeCl}_3 \cdot 6\text{H}_2\text{O}} 2a + \text{(2-methylindole)}$$

76%   64%

anti-inflammatory[16] activities. However, most of the known methods required harsh reaction conditions and multistep procedures.[17] Thus the development of a general and efficient synthesis of xanthenes is highly attractive.

We chose FeCl$_3$·6H$_2$O as catalyst for the following reactions. The present method could be applied successfully to various 2-aryloxybenzaldehydes (Table 2). In general, the reactions are rapid at 50 °C and the corresponding xanthenes **2b−h** were formed in 61−94% yield within 1−4 h. For example, the reactions of **1a** with 2-methylindole afforded xanthene **2b** smoothly in 87% yield (entry 1). The Ar^2 ring with phenyl- or 2-naphthyl group resulted in the formation of **2c** and **2d** in high yields of 82% and 79%, respectively (entries 2 and 3). However, Ar^2 ring substituted with a −NMe$_2$ group, namely, 2-(4-(dimethylamino)phenoxy)benzaldehyde (**1d**), resulted in no reaction with 2-methylindole. Substitution on the Ar^1 ring with a chlorine or a −NO$_2$ group gave rise to the substituted xanthenes **2e** and **2f** in 94% and 76% yields, respectively (entries 4 and 5). C-2-phenyl-substituted indole could also be used in this reaction, furnishing **2g** in 73% yield (entry 6). When *N*-methylindole was employed, a higher reaction temperature (100 °C) and higher catalyst loading (50%) were required; under these conditions, the desired xanthene **2h** was obtained in a satisfactory yield of 61% (entry 7).
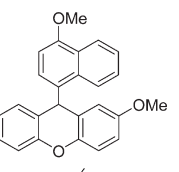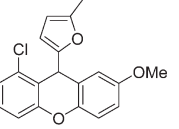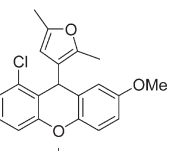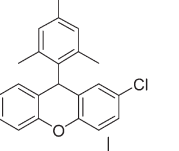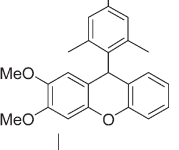
Several reaction pathways might be involved in the reaction. To elucidate the reaction mechanism, the reaction of **1a** and 1,2-dimethyl-1*H*-indole was quenched at 30 min. Interestingly, it was found that the bis(1*H*-indol-3-yl)methane **3a** was obtained as a major product in 36% yield along with 10% xanthene **2a** and 27% of unreacted starting aldehyde **1a**. The results indicated that the xanthene derivative **2a** might be formed through iron-catalyzed transformation of the triaryl-methane **3a**. It puzzled us, however, since if it is true, a C−C bond cleavage reaction in **3a** must occur, and the released indole could also be reused as substrate to enter the addition sequence with aldehyde. As a matter of fact, only 1.2 equiv of indole derivatives were sufficient in our reaction. We then carried out the reaction of **3a** in the presence of 10 mol % of FeCl$_3$·6H$_2$O; to our delight, it was found that the same xanthene **2a** was isolated in 76% yield, and the 1,2-dimethyl-1*H*-indole was also produced in 64% yield (Scheme 2). The results strongly supported our assumption that **2a** was formed through Fe(III)-catalyzed C−C bond cleavage of **3a** and subsequent cyclization in the one-pot procedure.

The fragmentation of triarylmethanes has been observed in several reports.[18] As known, the acid-catalyzed Friedel−Crafts alkylation of arenes with aromatic

of xanthenes was confirmed by X-ray crystallographic analysis of **2c** (see Table 2, entry 2).[9] Xanthene derivatives are of significant synthetic interests since they can be applied as luminescent dyes,[10] photochromic and thermochromic agents,[11] laser dyes,[12] as well as fluorescent materials for visualization of protease activities[13] etc. They also exhibit a variety of biological activities such as antibacterial,[14] antiviral,[15] and

(9) CCDC-727316 (compound **2c**) and CCDC-727317 (compound **2k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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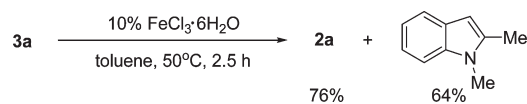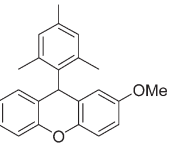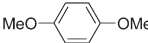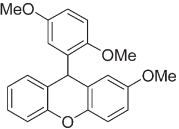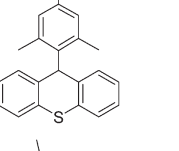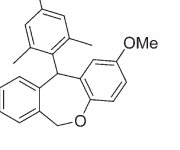
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TABLE 3.   Iron-Catalyzed Domino Process to Substituted Xanthenes and Its Analogues

| entry	ArCHO	Ar-H	product		yield(%)[a]
1	**1a**			**2i**	83[b]
2	**1a**			**2j**	54[c]
3	**1a**			**2k**	95
4	**1e**			**2l**	61[c,d]
5	**1e**			**2m**	69[e]
6	**1g**			**2n**	74[b]
7	**1h**			**2o**	63[b,f]
8	**8**			**9**	88[b]
9	**10**			**11**	48[b]

[a] Isolated yield. Unless noted, all the reactions were carried out at 50 °C for 1 h with 10 mol % of FeCl$_3$ 6H$_2$O, 4.0 equiv Ac$_2$O, and 1.2 equiv of arenes in toluene. [b] Mesitylene was used as solvent. [c] 2.0 equiv of arene was used. [d] DCE was used as solvent in a sealed tube at 120 °C, and 30 mol % of FeCl$_3$·6H$_2$O was used. [e] CH$_2$Cl$_2$ was used as solvent in a sealed tube. [f] 50 mol % of FeCl$_3$·6H$_2$O was used.

aldehydes has been known for a long time.[19] The earlier studies have shown that the Lewis acids such as AlCl$_3$-promoted reactions usually afford several products such as triarylmethanes, diarylmethanes, triarylmethanol, and anthracenes which have received a little attention. In a deep study, Roberts pointed out that excess AlCl$_3$ or Brønsted acids are able to induce the dealkylations and realkylations of triarylmethane intermediates that lead to mixed diarylmethanes and triarylmethanes in the reactions of aromatic aldehydes with arenes.[18a] Recently, a C−C bond cleavage has also been observed in the electrophilic activation of a borane complex Et$_3$N·BH$_3$ with trityl tetrakis(pentafluorophenyl)borate.[18c] A mechanism involving electrophilic substitution at an ipso carbon followed by fragmentation

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SCHEME 3

Ar³=1,2-dimethyl-1*H*-indol-3-yl
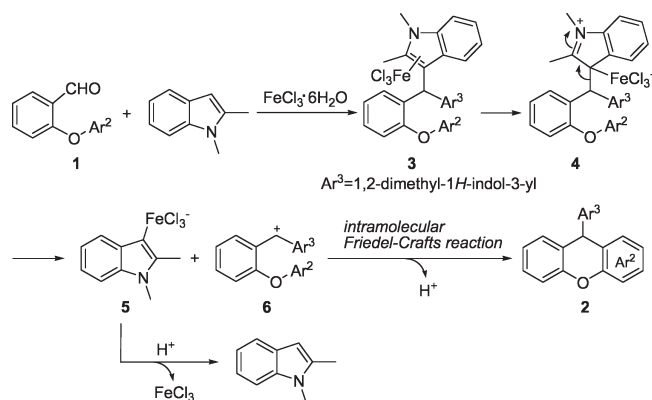
to Ph₂CH⁺ was proposed. Borane complex was also suggested to act as an electrophile, which may contribute to the C−C bond cleavage. On the basis of the above results and the known chemistry of triarylmethane, we tentatively propose a mechanism for this tandem sequence as depicted in Scheme 3. The reaction is initiated by Fe(III)-assisted double Friedel−Crafts alkylations to afford 1-arylbis(1*H*-indol-3-yl)methane **3**, then an electrophilic aromatic substitution occurs on the indole ring by attack of C-3 to yield an ionic intermediate **4**, this is followed by C−C bond cleavage to generate dibenzylic cation **6**, which undergoes intramolecular Friedel−Crafts reaction to give the product **2**. Protonation of the iron-adduct **5** would produce indoles for reuse.

Encouraged by these results, we proceeded to explore the cyclization reactions of aldehyde **2** with other arenes and heteroarenes. The results are shown in Table 3. It should be noted that in all of cases, the addition of 4.0 equiv of Ac₂O were needed.[20,21] Under the appropriate reaction conditions, a variety of 2-aryloxybenzaldehydes and arenes could be used in this domino reaction, furnishing the corresponding xanthenes **2i−o** in moderate to high yields of 54−95% (Table 3, entries 1−7).[22] Electron-rich arenes such as mesitylene, 1,4-dimethoxybenzene, and 1-methoxynaphthalene are all compatible with the reaction conditions. The regioselectivity of **2k** has been confirmed by X-ray crystallographic analysis.[9] The heteroarenes of 2-methylfuran and 2,5-dimethylfuran afforded xanthenes **2l** and **2m** successfully in 61% and 69% yields, respectively (entries 4 and 5). Note that a higher temperature of 120 °C and 30 mol % of iron catalyst were required to achieve a good yield in the case of 2-mehylfuran. When the reaction was carried out at 50 °C in the presence of 10 mol % of FeCl₃·6H₂O, the bis-(5-methylfuran-2-yl)methane, namely, 5,5′-((2-chloro-6-(4-methoxyphenoxy)phenyl)methylene)bis(2-methylfuran) **7** was obtained in 78% yield as a major product (2 equiv of 2-methylfuran was used). The C−C bond cleavage in **7** could also be observed by the reaction of **7** with 30 mol % of FeCl₃·6H₂O at 120 °C, in which the same xanthene **2l** was isolated in 55% yield. The efficiency of iron catalysis has been

extended to the synthesis of xanthene analogues. For example, biologically interesting thioxanthene **9** and a 7-membered oxacycle **11** have been prepared in 88% and 48% yields, respectively (entries 8 and 9).[23] The mechanism for most of these reactions might be different from that for indoles.[24] It may proceed through the first formation of diacetate followed by inter- and intramolecular Friedel−Crafts reactions to afford the desired products.[3g]

Conclusion

In summary, we have succeeded in developing an efficient, general, and one-pot procedure for the synthesis of multi-substituted xanthene derivatives through Fe(III)-catalyzed reaction of 2-aryloxybenzaldehydes with electron-rich arenes. This method offers several advantages such as high selectivities, mild reaction conditions, and easily accessible starting materials. Interestingly, a mechanistic study revealed that a novel C−C bond cleavage of a triarylmethane intermediate might be involved in the domino process. Further studies to elucidate the reaction mechanism and to extend the scope and synthetic utility are in progress in our laboratory.

Experimental Section

A Typical Procedure for the FeCl₃·6H₂O-Catalyzed One-Pot Synthesis of Xanthenes from the Reactions of Arenes with 2-Aryloxybenzaldehydes. A mixture of 2-(4-methoxyphenoxy)-benzaldehyde **1a** (57 mg, 0.25 mmol), 1,2-dimethyl-1*H*-indole (44 mg, 0.3 mmol), and FeCl₃·6H₂O (6.7 mg, 10 mol %) in toluene (3 mL) was stirred at 50 °C for 3 h. Then the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) to afford 3-(2-methoxy-9*H*-xanthen-9-yl)-1,2-dimethyl-1*H*-indole **2a** as a white solid in 84% isolated yield. Alternatively, after the reaction was complete, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the desired products. Mp 65−67 °C. ¹H NMR (400 MHz, d_6-DMSO, Me₄Si) δ 2.45 (s, 3H), 3.50 (s, H), 3.60 (s, 3H), 5.61 (s, 1 H), 6.38 (d, J = 2.4 Hz, 1H), 6.68 (t, J = 7.2 Hz, 1H), 6.74 (dd, J = 9.0, 2.8 Hz, 1H), 6.82−6.93 (m, 4H), 7.05−7.11 (m, 3H), 7.26 (d, J = 8.0 Hz, 1H); ¹³C NMR (100.6 MHz, d_6-DMSO, Me₄Si) δ 9.9, 29.3, 33.6, 55.1, 109.0, 112.8, 114.2, 114.6, 115.7, 116.5, 117.7, 118.4, 120.1, 122.8, 123.6, 125.0, 125.5, 127.5, 129.5, 133.9, 136.5, 144.5, 150.6, 154.8. HRMS (EI) for C₂₄H₂₁NO₂ [M⁺] calcd 355.1572, found 355.1573.

Supporting Information Available: Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallography of compounds **2c** and **2k**. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) For the effect of additives, see refs 3g and 3h.

(21) We have reported that benzyl acetates are better substrates compared with that of benzyl alcohols in various acid-catalyzed Friedel−Crafts reactions, see refs 5a−c.

(22) For entry 3, we also tried the reaction using 5% TsOH·H₂O in the presence or absence of Ac₂O; however, no desired product was observed, and most of the starting material remained.

(23) According to ¹H NMR spectra, compounds **2n** and **2o** have diastereotopic methyl groups, while compound **11** appears not to, and compound **9** has broad methyls.

(24) In most cases with the use of Ac₂O, we did not observe the intermediates of triarylmethane.