**Abstract:** Xanthene derivatives have broad applications in medicines, fluorescent probes, dyes, food additives, etc. Therefore, much attention was focused on developing the synthetic methods to prepare these compounds. Binaphthyl-based xanthene derivatives were prepared through the oxidation of BINOLs promoted by the hypervalent iodine reagent iodosylbenzene (PhIO). Nine-membered lactones were obtained through a similar oxidative reaction when iodoxybenzene (PhIO₂) was used. Additionally, one-pot reactions of BINOLs, PhIO and nucleophiles such as alcohols and amines were also investigated to provide alkoxylated products and amides in good to excellent yields.

Figure 1. Commercially available xanthene derivatives.

Xanthene is an oxygen-containing heterocycle featuring a dibenzopyran nucleus. Xanthene derivatives have attracted considerable attention due to their applications in fluorescent probes,[11] as laser dyes,[12] in medicines[13] and as food additives.[14] Therefore, these compounds play an important role in pharmaceutical[15] and industry areas.[16] For example, Fluorescein is a common probe for detecting H₂O₂ in living cells,[17] Rhodamine 6G is a classic reference dye to evaluate the efficiency of other dyes,[18] Blumeaxanthene is a traditional Chinese herb to treat gynecological disorders,[19] and Phloxine is generally used as a colorant in sweets, biscuits, ice creams etc. (Figure 1). [20]

Much attention was focused on exploring synthetic methods to prepare xanthene derivatives. The first one dates back to 1871, in which fluorescein was prepared by the condensation reaction between resorcinol and phthalic anhydride.[21] Since then, various methods have been developed to synthesize these compounds,[22] which mainly focus on exploring different substrates, designing novel catalysts and leveraging new technology. Taking typical research results in the last year as examples, the complex \([\text{IC}(\text{H}_3)\text{PCy}_3](\text{CO})\text{RuH})\text{BF}_4\) was used as a catalyst for the reaction of phenols and aldehydes,[23] In(OTF)₃ was employed to catalyze the coupling of 1,4-quinones with oxindoles,[24] nano-capsule \(\text{Fe}_3\text{O}_4@\text{Al}_2\text{O}_3@\text{SiO}_2@\text{Fe}_5\text{O}_3\) were prepared to catalyze the condensation of benzaldehyde and 2-naphthol[25] \(\text{K}_2\text{S}_2\text{O}_8\) was used as a promoter to achieve the reaction of 2-aryloxy phenylacetylenes with phosphine oxides,[26] \(\text{TiCl}_4\) was used for the cyclization of 2-aryloxybenzaldehydes,[27] \(\text{Cu(OAc)}_2\) was shown to catalyze the reaction of propargyl amines with 2-hydroxynaphthalene-1,4-diones[28] and others.[29]

Among the synthetic methods to prepare xanthene derivatives, the oxidation of BINOLs mediated by copper salt and amines is a straightforward way to synthesize binaphthyl-based xanthene derivatives. Xu and coworkers reported the copper salt mediated oxidation of BINOLs in apotic solvents.[30] In their study, two xanthene derivatives were obtained about 60% yield over 60 h. Six years later, Wulff and coworkers presented a copper-mediated deracemization of the \(C_2\)-symmetric compounds while xanthene derivatives were isolated as side products in low yields (Scheme 1a).[31] As these methods have several drawbacks, such as low yields and limited substrate scope, it is still necessary to develop better methods for preparing binaphthyl-based xanthene derivatives.

Hypervalent iodine reagents are mild oxidants and enable different functionalizations in an achiral or chiral manner.[32] We are interested in designing and synthesizing chiral hypervalent iodine compounds and using them in asymmetric oxidation transformations.[33] In a recent research, BINOL was used as chiral ligand to react with iodosylbenzene, expecting to obtain...
a binaphthyl-based chiral hypervalent iodine compound. However, the expected product was not formed, but products 3a and a nine-membered ketone lactone 4, which had been reported earlier (Scheme 1b), were observed instead. Herein, we present the oxidation of BINOLs mediated by hypervalent iodine reagents. On the one hand, xanthene derivatives 3 were obtained as the main product when iodosylbenzene 2a was used as oxidant, on the other hand, nine-membered ketone lactones 4 were generated when iodoxybenzene 2d was reacted with BINOL (Scheme 1c). In comparison to the former methods, this approach has many valuable merits such as mild reaction conditions, simple operation, short reaction times, high yields, and a broad substrate scope.

Initially, BINOL 1a was treated with 2.2 equivalents of iodosylbenzene 2a at room temperature and xanthene 3a was obtained in 46% yield accompanied with the formation of the nine-membered lactone 4a, which was also confirmed by X-ray crystallography (Table entry 3). It was noted that a decrease of the amount of 2a, 3a was also obtained in similar yield, but the reaction time was prolonged from 30 minutes to 6 h (Table 1, entries 4–5). Then, different solvents were examined. The reaction occurred well in aprotic solvent such as halogenated solvents, ethers and benzenes (Table 1, entries 6–13). The optimal solvent was 1,2-dichloroethane (DCE) which gave 3a in 80% yield. When alcohols were used, low yields were observed and the cyclization/alkoxylation product (see Table 4) was isolated as well.

### Table 1. Optimization of the reaction conditions to 3a.

| Entry | Hypervalent iodine reagent 2 | Ratio | Solvent | Temperature °C | 3a Yield [%] |
|-------|------------------------------|-------|---------|---------------|-------------|
| 1     | Ph—I—O 2a                    | 1:2   | CHCl₃   | 20            | 46          |
| 2     | Ph—I—O 2a                    | 1:2.5 | CHCl₃   | 20            | 66          |
| 3     | Ph—I—O 2a                    | 1:3   | CHCl₃   | 20            | 28          |
| 4     | Ph—I—O 2a                    | 1:1.5 | CHCl₃   | 20            | 64          |
| 5     | Ph—I—O 2a                    | 1:1   | CHCl₃   | 20            | 60          |
| 6     | Ph—I—O 2a                    | 1:2.5 | CHCl₂   | 20            | 74          |
| 7     | Ph—I—O 2a                    | 1:2.5 | THF     | 20            | 64          |
| 8     | Ph—I—O 2a                    | 1:2.5 | Et₂O    | 20            | 53          |
| 9     | Ph—I—O 2a                    | 1:2.5 | CH₃CN   | 20            | 47          |
| 10    | Ph—I—O 2a                    | 1:2.5 | toluene | 20            | 60          |
| 11    | Ph—I—O 2a                    | 1:2.5 | benzene | 20            | 61          |
| 12    | Ph—I—O 2a                    | 1:2.5 | acetone | 20            | 74          |
| 13    | Ph—I—O 2a                    | 1:2.5 | CICH₂CH₂Cl (DCE) | 20 | 80          |
| 14    | Ph—I—O 2a                    | 1:2.5 | methanol | 20 | 20          |
| 15    | Ph—I—O 2a                    | 1:2.5 | ethanol  | 20            | 11          |
| 16    | Ph—I—O 2a                    | 1:2.5 | water    | 20            | 0           |
| 17    | Ph—I—O 2a                    | 1:2.5 | water/DCE | 20 | 53          |
| 18    | Ph—I(OCOCH₃) twenty 2b       | 1:2.5 | DCE     | 20            | 45          |
| 19    | Ph—I(OCOCF₃) twenty 3c       | 1:2.5 | DCE     | 20            | 40          |
| 20    | Ph—IO₂—d                    | 1:2.5 | DCE     | 20            | 22H        |
| 21    | Ph—I—O 2a                    | 1:2.5 | DCE     | 0             | 47          |
| 22    | Ph—I—O 2a                    | 1:2.5 | DCE     | reflux        | 29          |

[a] Reactions were carried out with 0.17 mmol 1a in 2 mL of solvent. [b] 76% compound 4a was isolated as well.
as dibromo, dichloro, diiodo substituents at the same position (Table 2, 3b–3f).

Unfortunately, when 3,3'-diester substituted BINOL was used, the reaction does not occur because of stronger electron withdrawing effects of the ester group. Then, 6,6'-dibromo, 7,7'-dimethoxy and 7,7'-dibromo substituted BINOLs were employed, the target products were generated in 78%, 71% and 69% yield, respectively (Table 2, 3g–3i). The X-ray crystallographic analysis of 3i further confirmed the structure of the product. Monosubstituted non-C$_2$-symmetric BINOLs were examined as well. It was found that 3-monosubstituted BINOLs such as 3-bromo, 3-iodo and 3-methyl substituted BINOLs gave the target product 3j–3l in good yields with excellent chemoselectivity (Table 2). The steric hindrance in the ortho position will stop the attack of oxygen to the aromatic carbon. On the other hand, when 7-monosubstituted such as 7-bromo, 7-methoxyl BINOLs were used, product mixtures were observed. Due to the steric hindrance in ortho position, the ratio of isomers 3m:3m' was 2:1. Similar results were found for isomers 3n and 3n' with a 3:1 ratio (Table 2). Disubstituted non-C$_2$-symmetric BINOLs were also investigated. 7-Methoxyl-6'-ester substituted BINOL gave desired product 3o in 73% yield exclusively. But 7-bromo-3'-ester BINOL gave an isomer mixture of 3p and 3p' in a 1:5 ratio (Table 2).

The generality of the oxidative transformation of BINOLs mediated by iodoxybenzene 2d to form nine-membered lactones was investigated. BINOLs possessing 3,3'-dichloro, dibromo, dimethylester, dimethyl and di-TMS groups gave the target products in good to excellent yield in DCE at room temperature (Table 3, 4b–4f). It was noted that 3,3'-diester substituted BINOL, which cannot be oxidized by 2a, reacted with 2d to provide product 4d in 81% yield, indicating that the electron withdrawing group in BINOLs doesn't greatly affect the oxidation of BINOLs mediated by 2d. The structure of the product was further confirmed by X-ray crystallography of 4a and 4e. 6,6'-Dibromo, 6,6'-diphenyl, 7,7'-dibromo and 7,7'-dimethoxyl substituted BINOLs can also be oxidized by 2d affording 4g–4j in 71–84% yield (Table 3, 4g–4j). When non-C$_2$-symmetric BINOLs with different substitute on different position such as 3-bromo, 3-iodo, 7-bromo, 7-methoxyl and 7-bromo-3'-ester were used, all of them gave the corresponding products exclusively except for 3-iodo substituted BINOL which gave the isomeric mixture 4l and 4l' in a 10:1 ratio (Table 3, 4k–o).

**Table 2.** Synthesis of xanthene derivatives 3.[a]

| R' | R'' | R''' |
|----|-----|------|
| Br | Br  | Br   |
| Br | Me  | Me   |
| Br | TMS | TMS  |

[a] Reactions were carried out with 0.17 mmol of 1 and 0.43 mmol of 2a in 2 mL of DCE.

**Table 3.** Synthesis of nine-membered lactones 4.[a]

| R' | R'' | R''' |
|----|-----|------|
| Br | Br  | Br   |
| Br | Me  | Me   |
| Br | TMS | TMS  |

[a] Reactions were carried out with 0.17 mmol of 1 and 0.43 mmol of 2d in 2 mL of DCE.
As described in Table 1 (entries 14–15), when BINOL was oxidized by 2a in the presence of an alcohol, the cyclization-alkoxylation compounds 5 were obtained as main products. The synthesis of 5 has been reported\(^{[25]}\) and some derivatives have been reported to possess bioactivities.\(^{[5a,25c]}\) Therefore, we turned our attention to investigate the oxidation of BINOLs mediated by 2a in the presence of alcohols to form compounds 5. Treatment of BINOL 1a with 2a in different alcohols formed the corresponding products 5a–j in moderate to good yields (Table 4, 5a–j). Specifically, linear primary alcohols from methanol to hexanol can provide the desired product 5a–f in 57–71% yields. The structure of these products was further confirmed by X-ray crystallographic analysis of 5a and 5c.\(^{[24]}\) The chain length of alcohols does not greatly affect the reaction yield. Branched primary alcohols such as isobutyl alcohol also reacted well with BINOL in the presence of 2a and compound 5g was obtained in 76% yield. When secondary alcohols such as isopropanol was used, the target compound 5h was also produced in 50% yield. Unfortunately, tertiary alcohols do not provide products due to the steric hindrance. Allyl alcohol also gave the corresponding product 5j in good yield. But when electron-poor alcohols such as TFE and HFIP were used, only trace amounts of products were observed (Table 4, 5k–l). 6,6′-Dibromo and 7,7′-dibromo substituted BINOLs were selected as C\(_2\)-symmetric BINOLs and the desired compounds 5m and 5n were obtained in 69% and 74% yield, respectively. Non-C\(_2\)-symmetric 7-bromo substituted BINOL was applied to react with 2a in methanol and the target product 5o was obtained in 69% yield.

According to the above results that alcohols can be used as a nucleophile to react with BINOLs in the presence of 2a in one-pot manner to afford products 5, we assumed that amines would also be able to react with BINOL to produce similar products 6. Thus, dimethylamine, diethyl amine and morpholine were selected as nitrogen-containing nucleophiles to react with 1a under the reaction conditions. However, products 6 were not observed but products 7a–c were formed (Scheme 2). The structures of 7a and 7b were also confirmed by X-ray crystallography.\(^{[24]}\) Products 7 are derived from the oxidation of 1a to form 4a, followed by hydrolysis under basic condition to yield 10, which then reacted with the amine to produce amide 7. Ethanethiol and thiophenol were also selected as possible nucleophiles to react with BINOL mediated by 2a but no reactions were observed.

Further transformations of 3a and 4a are illustrated in Scheme 3. Treatment of 3a with NaBH\(_4\) in THF allows a selective reduction of the unsaturated ketone in 3a and product 8 was obtained in 75% yield.\(^{[24]}\) Due to the existence of the α,β-unsaturated carbonyl skeleton in 3a, a Michael addition would occur on the unsaturated alkyne. In order to achieve this, we selected ethanethiol and thiophenol as possible nucleophiles to react with BINOL mediated by 2a, but no reactions were observed.

**Table 4.** Oxidative cyclization and alkoxylation of BINOLs.\(^{[4]}\)

| Compound | Reaction | Yield (%) |
|----------|----------|-----------|
| 5a | 67% |
| 5b | R = ethyl, 62% |
| 5c | R = n-propyl, 57% |
| 5d | R = n-butyl, 59% |
| 5e | R = n-pentyl, 71% |
| 5f | R = n-hexyl, 63% |
| 5g | R = i-butyl, 76% |
| 5h | R = iso-propyl, 50% |
| 5i | R = t-butyl, trace |
| 5j | R = ethyl, 64% |
| 5k | R = CF\(_3\)CH\(_2\), trace |
| 5l | R = (CF\(_3\))\(_2\)CH, trace |

[a] Reactions were carried out with 0.17 mmol of 1 and 0.43 mmol of 2a in 2 mL of alcohol.

**Scheme 2.** Amines as nucleophile in the oxidation of BINOL with iodosylbenzene 2a.

**Scheme 3.** Synthetic utility of 3a and 4a.
occurred between 3a and dimethyl malonate under basic reaction conditions to provide product 9 in 78% yield. The synthetic utility of 4a was also investigated by exposure to a solution of NaOH in THF/water (1:1) and (Z)-product 10 was obtained in 89% yield through hydrolysis of 4 by nucleophilic addition to the lactone which doesn’t affect the original geometry of C=C bond. Interestingly, treatment of 4a with NaBH₄ in THF formed the (E)-product 11 in 83% yield. We assumed that the reduction of 4a by NaBH₄ occurred through the attack of hydride to both carbonyl groups. The initial reduction of the ketone to the secondary alcohol could trigger a subsequent Michael addition to the α,β-unsaturated lactone leading to an isomerization of the C=C double bond to decrease the steric hindrance in 11 during reduction of the lactone.

To gain further insight into the mechanism of the oxidative reaction of BINOLs mediated by hypervalent iodine reagents, several additional experiments were conducted. The target products 3 and 4 cannot be obtained without the hypervalent iodine reagents, but replacing the nitrogen atmosphere with air or adding TEMPO as a radical scavenger did not affect the reaction yield. We could prove that compound 3 is not an intermediate in the formation of 4 and 5 as it does not react with iodoxybenzene 2d with or without the presence of methanol or dimethylamine. This suggests that 4 and 5 are not derived from 3 (Scheme 4a). However, carboxylic acid 10 can react with dimethyl amine to form 7a in 80% yield (Scheme 4b).

Based on the control experiments and literature, a mechanism for the formation of 3a and 5 is proposed in Scheme 5. After addition of BINOL 1a to iodosylbenzene 2a, iodine(III) intermediate 12 is formed. Iodine(III) intermediate 13 was obtained through intramolecular tautomerism of the enol and addition to iodine. Finally, intermediate 13 underwent reductive elimination to form intermediate 14, which subsequently aromatizes to afford 15. After addition of 2a to 15, iodine(III) intermediate 16 is formed which is then reacting with water or alcohols to deliver products 3a and 5 accompanied with the elimination of iodosobenzene and water. When chiral (R)-BINOLs 1 are used as substrates for the reaction with iodosylbenzene 2a in either DCE or alcohols (seeing Supporting Information), the resulting products have very low enantioselectivities. As the stereogenic axis of 1 is destroyed in the formation of intermediate 14, which is reacting with nucleophiles, very low enantiomeric excesses of xanthene derivatives 3 and 5 is obtained.

For the formation of 4a, the addition of 2d to 1a gave rise to iodine(V) intermediate 17, which deaeromatized by the attack of water as a nucleophile to form 18. Intramolecular nucleophilic addition between the naphthyl hydroxyl to the carbonyl group in 18 led to an intermediate diol 19. Addition to PhIO occured to form iodine(III) intermediate 20, which was underwent reductive elimination to yield the final nine-membered lactone 4a.

In conclusion, a novel and facile method for preparing xanthene derivatives and nine-membered lactones through the oxidation of BINOL mediated by hypervalent iodine reagents is presented. Both electron-donating and electron-withdrawing substituted BINOLs, C₂-symmetric and non-C₂-symmetric BINOLs give products 3 and 4 in high yields. Especially for some non-C₂-symmetric cases, excellent chemoselectivities were observed. On the other hand, a one-pot method for the oxidation of BINOLs mediated by iodosylbenzene in the presence of alcohols or amines were explored, various cyclization/alkoxylation product 5 and α,β-unsaturated amides 7 were generated in good to
excellent yields. The subsequent synthetic transformations of products 3 and 4 were investigated, showing that these products may become interesting building blocks for organic synthesis.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: BINOL • hypervalent iodine reagents • lactones • oxidation • xanthenes

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