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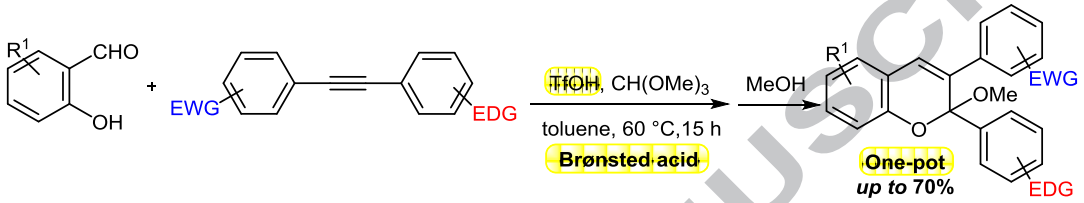

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Regioselective one-pot synthesis of 2,3-diaryl-2*H*-1-benzopyrans via Brønsted acid-catalyzed [4+2] cycloaddition of salicylaldehydes with diarylacetylenes

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ABSTRACT

A regioselective one-pot synthesis of 2,3-diaryl-2*H*-1-benzopyrans from easily available various diarylacetylenes and salicylaldehydes via Brønsted acid-catalyzed [4+2] cycloaddition has been developed. High regioselectivity was observed in the reaction to afford 2-(electron-rich aryl)-3-(electron-poor aryl)-2*H*-1-benzopyrans in good yields. The present reaction provides versatile access to functionalized 2,3-diaryl-2*H*-1-benzopyrans, which would be useful as key intermediates for the synthesis of biologically and photochemically active molecules.

1. Introduction

2,3-Diaryl-2*H*-1-benzopyrans are used as building blocks in the synthesis of a variety of bioactive compounds and applied to photochromic materials in academic and industrial fields. They are known to be an important skeleton in interesting compounds such as antiestrogens[1], post-coital contraceptive active compounds[2] and photochemically active molecules[3] (Figure 1).

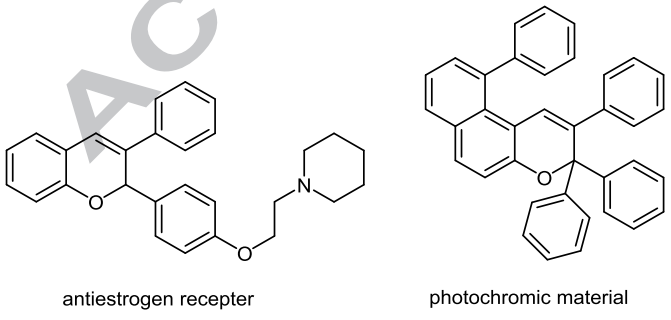
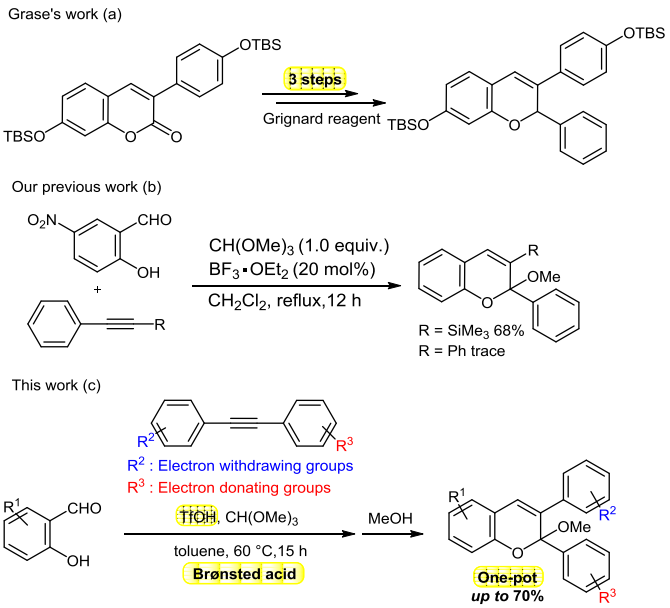


Figure 1 Selected examples of 2,3-diaryl-2*H*-1-benzopyrans

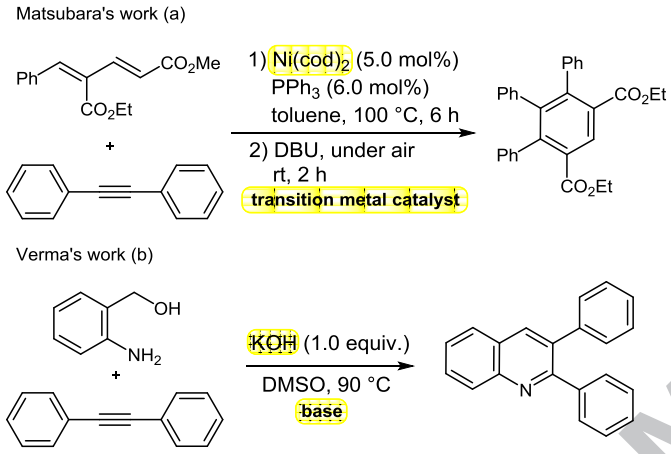
With this broad range of interesting properties and applications, the development of synthetic strategies for 2,3-diaryl-2*H*-1-benzopyran ring-system has received significant attention. The representative synthetic methods include base-catalyzed condensation of 4-hydroxybenzaldehyde with desoxybenzoins followed by reduction with sodium borohydride,[1a] reaction of 2-phenoxychromenes with Grignard reagents (Scheme 1a),[1f] nickel-catalyzed cross-coupling of chromene acetals with boronic acid,[4] Suzuki cross-coupling of aryl halides with phenylboronic acids.[3] Despite the availability of these existing methods, they usually suffer from multi-step synthesis, resulting in poor total yields of the desired products. Since bioactive compounds containing 2,3-diaryl-2*H*-1-benzopyran have a variety of substituent pattern, there remains a



Scheme 1 Synthesis of 2,3-diaryl-2*H*-1-benzopyrans

demand for general strategies that can more efficiently provide various substituted 2,3-diaryl-2*H*-1-benzopyrans.

Recently, transition metal-catalyzed [4+2] cycloaddition with diphenylacetylenes has been intensively investigated (e.g., Scheme 2a).[5] On the other hand, metal-free [4+2] cycloaddition of diphenylacetylene remains in the classical process, which requires harsh reaction conditions such as high pressure and high temperature.[6] It suggests that diphenylacetylene has low reactivity toward Diels-Alder reaction. An interesting work on base-promoted intermolecular [4+2] cycloaddition of diphenylacetylenes was reported by Verma and co-workers in 2016 (Scheme 2b).[7] The literature survey revealed that metal-free, acid-promoted intermolecular [4+2] cycloaddition of diarylacetylenes for the synthesis of chromenes remains elusive.



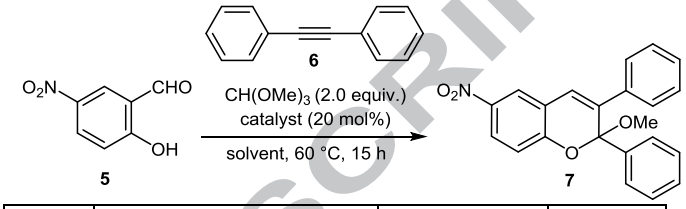
Scheme 2 intermolecular [4+2] cycloaddition of diphenylacetylenes

Very recently, we have investigated a direct synthesis of 3-silylchromenes by [4+2] cycloaddition of *in situ* generated *o*-quinonemethides with alkynyl silanes.[8] In the course of this study we reported that salicylaldehydes react with alkynylsilanes in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ and trimethyl orthoformate at reflux to give 3-silylchromenes in moderate yields. However, diphenylacetylene, which has symmetrical distribution of electron density, was subjected to this reaction condition to give a trace amount of the desired chromene (Scheme 1b). This negative result prompted us to develop metal-free, acid-promoted intermolecular [4+2] cycloaddition of various diarylacetylenes for the synthesis of 2,3-diaryl-2*H*-1-benzopyrans. Herein, we report a regioselective one-pot synthesis of 2,3-diaryl-2*H*-1-benzopyrans from various diarylacetylenes via Brønsted acid-catalyzed [4+2] cycloaddition in the presence of trimethyl orthoformate (Scheme 1c).

2. Results and discussion

We initially investigated the reaction of 5-nitrosalicylaldehyde with diphenylacetylene in the presence of acid catalysts in various solvents (Table 1). When polar solvents like DMF, acetonitrile, THF, CH_2Cl_2 were used, the reactions did not proceed smoothly (entries 1-4). However, several non-polar solvents such as benzene and toluene, all led to the formation of desired product **7** in moderate yields (entries 5 and 6).[9] In those cases, byproducts **8** and **9** were isolated in low yields (4% and 12%, respectively) (Figure 2). When other Brønsted acids like benzenesulfonic acid and $HBF_4{\cdot}OEt_2$ were used instead of TfOH, the desired product was obtained in moderate yields (entries 7 and 8). In contrast, using a catalytic amount of Lewis acids such as $BF_3{\cdot}OEt_2$ and $Sc(OTf)_3$, the yields of product **7** decreased (entries 9 and 10). Finally, when excess MeOH was added during the work-up procedure, the best yield of the product could be obtained in 52% yield (entry 11).

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Yield (%)
1	TfOH	DMF	N.R
2	TfOH	THF	2
3	TfOH	Acetonitrile	2
4[b]	TfOH	CH_2Cl_2	9
5[b]	TfOH	Benzene	23
6	TfOH	Toluene	38
7	Benzenesulfonic acid	Toluene	29
8	$HBF_4{\cdot}OEt_2$	Toluene	14
9	$BF_3{\cdot}OEt_2$	Toluene	16
10	$Sc(OTf)_3$	Toluene	10
11[c]	TfOH	Toluene	52

[a] All reactions were carried out with **5** (2.0 mmol), **6** (1.0 mmol), $CH(OMe)_3$ (2.0 equiv.), and catalyst (20 mol%) in solvent (5.0 mL) under nitrogen. [b] reflux [c] MeOH (5.0 mL) was added during work-up.

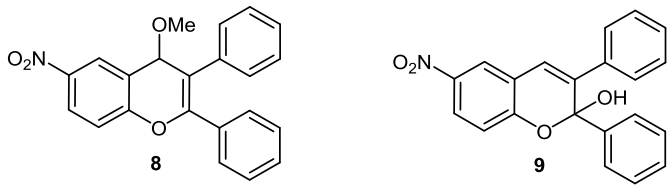
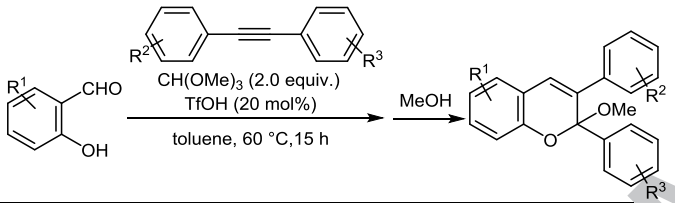


Figure 2 Byproducts of the reaction

With the optimal reaction condition in hand, the combination of salicylaldehydes and diarylacetylenes was explored to examine the generality of the reaction (Table 2). Various salicylaldehydes with electron withdrawing groups gave the corresponding products in moderate yields (entries 1 and 2). However, substrates having moderately electron withdrawing substituent, 4-bromo- and 4-acetoxy-salicylaldehydes, did not give the desired products (entries 3 and 4). *p*-Tosyloxysalicylaldehyde afforded the desired product in low yield (entry 5). On the other hand, salicylaldehyde with electron donating group did not afford the desired product (entry 6).

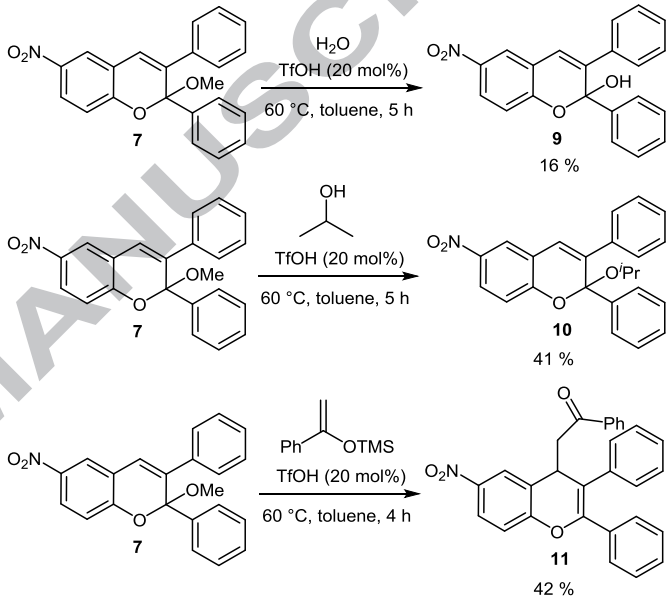
When various diarylacetylenes with electron withdrawing groups were used, the corresponding adducts were formed in moderate yields with high regioselectivity (entries 7-9). The reactions with a variety of diarylacetylenes possessing electron donating substituents smoothly underwent to give the corresponding products in good yields (entries 10-12, 14-16). However, 1-methoxy-3-(phenylethynyl)benzene failed to participate in the reaction (entry 13). Good yields were obtained when the reaction of 5-nitrosalicylaldehyde with 1-methyl-4-(phenylethynyl)benzene and 1-isopropyl-4-(phenylethynyl)benzene was carried out, and the desired products were achieved in 69% and 70% yields, respectively (entries 16 and 17). The electronic bias of the ring/substituents on the C−C triple bond of the unsymmetrical alkynes plays an important role in the regioselective formation of 2*H*-1-benzpryrans.[10] Regioselectivity of all products was confirmed by the analysis of ^{13}C NMR shift data of the corresponding benzene rings, which were assigned by comparition with ^{13}C NMR data of the parent diarylchromene **7**, which was fully characterized by ^{1}H NMR, ^{13}C NMR, COSY, HMBC, HSQC, IR, and HRMS.[11]

Table 2 Reaction of salicylaldehydes with alkynes[a]



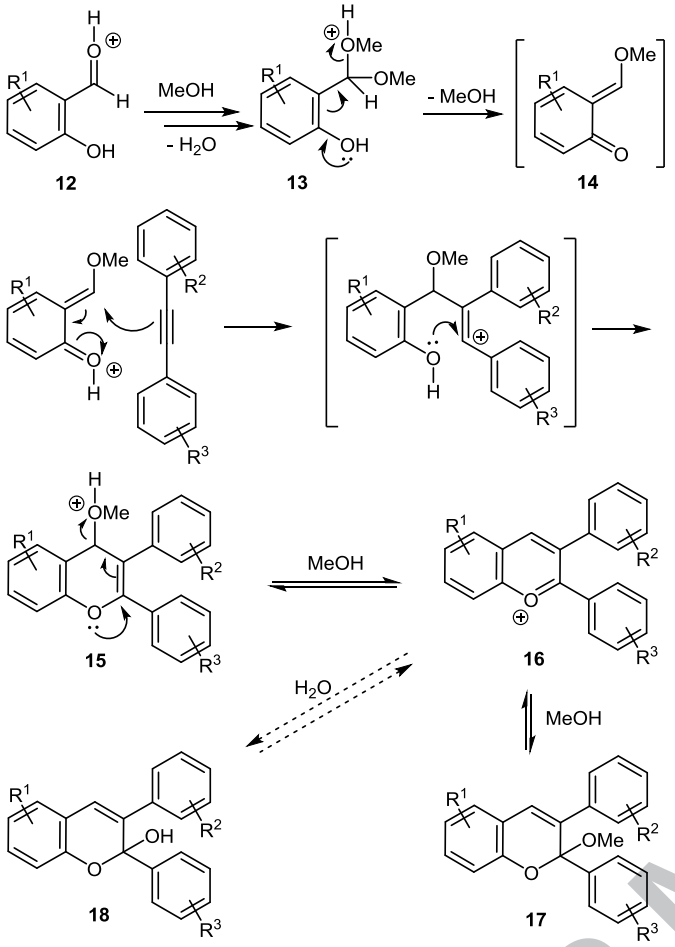
Entry	R^1	R^2	R^3	Yield (%)
1	5-NO_2	H	H	52
2	5-CO_2Me	H	H	14
3	4-Br	H	H	N.R
4	4-OAc	H	H	N.R
5	4-OTs	H	H	20
6	5-OMe	H	H	N.R
7	5-NO_2	4-NO_2	H	24
8	5-NO_2	4-CO_2Me	H	28
9	5-NO_2	4-CF_3	H	38
10	5-NO_2	4-NO_2	4-Me	54
11	5-NO_2	4-OMe	4-OMe	39
12	5-NO_2	H	2-OMe	47
13	5-NO_2	H	3-OMe	Trace
14	5-NO_2	H	4-OMe	52
15	5-NO_2	H	4-Ph	50
16	5-NO_2	H	4-Me	69
17	5-NO_2	H	4-^{i}Pr	70

Finally, we investigated further transformations of 2,3-diaryl-2*H*-1-benzopyrans at C-2 position (methoxy group) by various nucleophiles.[12,13] Treatment of H_2O or ^{i}PrOH, which are known as the Peason's hard nucleophiles, afforded the 2-substituted 2*H*-1-benzopyrans in 16% and 41% yields, respectively (Scheme 3). On the other hand, treatment of [1-[(trimethylsilyl)oxy]ethenyl]benzene, which is known as soft nucleophile, gave no 2-substituted product but 4-substituted 4*H*-1-benzopyran **11** in 42% yield. It is noted that these results indicate that this reaction is a good methods for constructing 2-substituted 2,3-diaryl-2*H*-1-benzopyrans and 4-substituted 2,3-diaryl-4*H*-1-benzopyrans, leading to the effective synthesis of biologically and photochemically active molecules.



Scheme 3 Examination of nucleophilic attack to 2,3-diaryl-2*H*-1-benzopyran 7

A plausible reaction mechanism for the cycloaddition of salicylaldehydes with diarylacetylenes is depicted in Scheme 4. First, acid-catalyzed acetal formation of salicylaldehydes **12** with MeOH from $CH(OMe)_3$ would occurred to afford the intermediates **13**, which is amenable to elimination of MeOH under acidic conditions, affording *o*-quinonemethides **14**. It is considered that *o*-quinonemethide may react with diarylacetylenes by stepwise mechanism to give cyclic products **15**. It is suggested that the step of attack of the more electron-rich carbon of unsymmetrical alkynes into the exo-methylene carbon of *o*-quinonemethide intermediates would determine the regioselectivity of the products.[14] Elimination of methoxy group from **15** with the assistance of Brønsted acid can form flavylium salts **16**, which would equilibrate with **17** under the reaction conditions. Then, attack of excess MeOH at 2-position of flavylium salts **16** would generate **17** as the most stable products. When the reaction mixture is quenched by aqueous work-up, nucleophilic water would compete with MeOH in the step of addition of nucleophile to **16**, leading to the reduction of the yields of the desired products.



Scheme 4 Plausible mechanism for the synthesis of 2,3-diaryl-2*H*-1-benzopyrans from various salicylaldehydes and diarylacetylenes

In summary, we have developed a regioselective one-pot synthesis of 2,3-diaryl-2*H*-1-benzopyrans from easily available various diarylacetylenes and salicylaldehydes via Brønsted acid-catalyzed [4+2] cycloaddition. Electron withdrawing or electron donating substituted aryl groups of diarylacetylenes induced the high regioselectivities by which 2-(electron-rich aryl)-3-(electron-poor aryl)-2*H*-1-benzopyrans were obtained. The substitution of methoxy group of the product by various nucleophiles led to 2-substituted 2,3-diaryl-2*H*-1-benzopyrans or 4-substituted 2,3-diaryl-4*H*-1-benzopyran skelton according to HSAB principle. Thus, the present reactions provide versatile access to functionalized 2,3-diaryl-2*H*-1-benzopyrans that would be a useful tool for the synthesis of biologically and photochemically active molecules.

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9. General procedure for the synthesis of 2-methoxy-6-nitro-2,3-diphenyl-2*H*-1-benzopyran (**7**): To a mixture of 5-nitrosalicylaldehyde (0.334 g, 2.0 mmol), diphenylacetylene (0.178 g, 1.0 mmol) and trimethyl orthoformate (0.212 mL, 2.0 mmol) in toluene under nitrogen, trifluoromethanesulfonic acid (0.0176 mL, 20 mol%) was added. After being stirred at reflux for 15 h, methanol (5.0 mL, 0.12 mol) was added. Then the reaction mixture was quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with ethylacetate. The combined organic layer were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane / ethylacetate = 100 : 1 to 20 : 1) to afford product **7**. It was identified by ^{1}H NMR, ^{13}C NMR, COSY, HMBC, HSQC, IR, and HRMS. Yield 52%, yellow solid. IR (neat): 3063, 2839, 1511, 1480, 1446, 1336, 1249, 1181, 1125, 1107, 1087, 1016, 987, 962, 903, 827, 772, 748, 697, 595, 566 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 2.6 Hz, 1H), 8.11 (dd, *J* = 2.6, 9.0 Hz, 1H), 7.44-7.55 (m, 2H), 7.31-7.35 (m, 2H), 7.17-7.31 (m, 7H), 7.15 (s, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 3.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3, 142.0, 140.7, 136.3, 134.7, 128.3, 128.1, 127.8, 126.5, 125.5, 124.7, 122.9, 119.7, 115.8, 105.2, 51.2. HRMS (ESI+): m/z calcd for $C_{21}H_{13}NO_3$ ([M-OMe]$^+$): 327.0895, found: 327.0911.
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13. General procedure for the synthesis of 6-nitro-2,3-diphenyl-2-isopropoxy-2*H*-1-benzopyran (**10**): To 2-methoxy-6-nitro-2,3-diphenyl-2*H*-chromene (**7**), (0.359 g, 1.0 mmol) in toluene under nitrogen, TfOH (0.018 mL, 20 mol%) was added and heated to 60 °C. Then 2-propanol (0.771 mL, 10 mmol) was added. After being stirred at 60 °C for 5 h, the reaction mixture was quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with ethylacetate. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane / ethylacetate = 100 : 1 to 20 : 1) to afford 6-nitro-2,3-diphenyl-2-isopropoxy-2*H*-1-benzopyran (**10**) (0.157 g, 41%) as a yellow solid. IR (neat): 3066, 2971, 1634, 1612, 1578, 1516, 1480, 1448, 1334, 1257, 1233, 1178, 1091, 1072, 1042, 1019, 971, 926, 910, 877, 833, 808, 757, 750, 695, 650, 589, 571 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.07 (dd, *J* = 2.6, 8.7 Hz, 1H), 7.47-7.63 (m, 2H), 7.32-7.40 (m, 2H), 7.17-7.32 (m, 6H), 7.16 (s, 1H), 6.91 (d, J = 9.0 Hz, 1H), 4.01-4.16 (m, 1H), 1.26 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.9, 141.7, 141.5, 136.4, 135.7, 128.6, 128.1, 128.0, 126.4, 125.3, 123.8, 122.8, 119.8, 115.9, 105.4, 68.2, 24.5, 23.3. HRMS (ESI+): m/z calcd for $C_{24}H_{22}NO_4$ ([M+H]$^+$): 388.1549, found: 388.1551.
14. (a) Coefficient values calculated by using Winmostar version 6.015 (MOPAC PM3) are shown in supplementary data. (b) N. Senda, *Idemitsu Tech. Rep*., **2006**, *49*, 106-111.

Highlights

Hightlights

- A regioselective one-pot synthesis of 2,3-diaryl-2*H*-1-benzopyrans has been developed.
- Brønsted acid-catalyzed [4+2] cycloaddition has been developed.
- High regioselectivity was observed in the reaction.
- The present reaction provides functionalized 2,3-diaryl-2*H*-1-benzopyrans.