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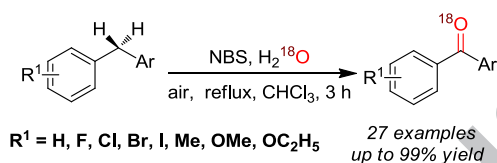


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Synthesis of structurally diverse diarylketones through the diarylmethyl sp^3 C-H oxidation

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ABSTRACT

Under open-flask conditions, an efficient method to assemble a series of diversely functionalized diarylketones in the presence of commercially available NBS has been developed. Yields of up to 99% have been achieved employing diarylmethanes as starting material. Based on ¹⁸O-labeled experiment, the addition of stoichiometric water eventually leads to excellent yields in all carbonylation cases.

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The C-H transformation of hydrocarbons has received more and more attention in the past decades, in which C-H bond can be activated generally in the presence of non-metal compounds, metal oxides and metal complexes.¹ C-H bond activation catalyzed by transition metals which proceed through oxidative addition, or oxidized by their oxides serving usually as oxygen sources has been considered to be an efficient and straightforward method for synthetic transformation from inert substrates.² In addition, oxidative non-metal compounds and elementary substances were employed in C-H bond activation processes for hydrocarbon functionalization, and the transformation proceeds through the general way of pyrolysis, light irradiation or radiolysis.³ This method provides an attractive synthetic strategy avoiding participation of transition metal ions with lower synthetic cost. However, such transformation usually suffers from heavy side-products, such as chain-lengthened alkanes, alkenes and alkynes, due to the stronger oxidability and lower selectivity of such oxidants.

Replacement of sp^3 C-H hydrogen by oxygen to prepare ketones, i.e. carbonylation, has been investigated intensively. It is well-known that diarylketones containing a vital carbonyl group can serve as valuable structural motif in drugs,⁴ such as (*S*)-ketoprofen, daunorubicin, sulisobenzone and pitofenone,⁵ as well as functional molecules,⁶ advanced materials,⁷ and useful synthetic intermediates in molecular transformations.⁸ In addition to direct C-H transformation, many strategies to prepare diarylketones have been exploited, including Friedel-Crafts acylation reaction,⁹ CO insertion reaction,¹⁰ and transition metal-

catalyzed coupling reaction.¹¹ Among these transformations, the agents which are moisture-sensitive and fragile to be oxidized are involved, therefore N₂ protection conditions are often required. Direct oxidation of diarylmethanes through C-H bond activation to prepare diarylketones employing oxidants has been exploited, in which the KBr, *N*-hydroxyphthalimide and co-oxidants such as oxygen, H₂O₂ and oxone are inexpensive, the reaction conditions are mild and the methods work on in a wide scope, i.e. both diarylmethanes and monoarylmethanes.^{12, 13, 14}

Elemental X₂ (X = F, Cl, Br and I) and halides (MX_n) were usually used as halogen sources in synthetic transformation.¹⁵ In reported works, utility of X₂ and halosuccinimides mainly leads to dihalogenation and monohalogenation, including allylic Wohl-Ziegler halogenation.¹⁶ The photochemical bromination of calixarene tetramethoxy ether and subsequent hydrolysis of the corresponding dibromo intermediate to ketone under spotlight irradiation have been reported, and Fisher et al have reported oxidation of calixarene to the respective tetraoxo derivative under bromosuccinimide (NBS) and UV irradiation conditions.¹⁷ However, to our best of knowledge, employing *N*-halosuccinimide as a halogenation/oxidation reagent, the effective transformation of diarylmethanes into diarylketones under sunlight irradiation combined with heat conditions through one-pot tandem halogenation-hydrolysis has not reported to date. Recently, we have developed a FeCl₃·6H₂O-promoted oxidative self-coupling reaction of anilines via a free radical mechanism.¹⁸ We herein report a convenient and efficient one-pot radical NBS halogenation-hydrolysis method under heat and natural light

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irradiation conditions for synthesis of various functionalized diarylketones from the corresponding diarylmethanes¹⁹ with short reaction time and simple operation procedure.

We firstly focused on the optimization of reaction conditions and the carbonylation of diphenylmethane was chosen as a model reaction with the results summarized in Table 1. The carbonylation product **3a** was obtained in low 36% yield under nitrogen atmosphere in the presence of 5.0 eq. of NBS (For the optimal amount of NBS and solvent, see supporting information) (entry 1) and under open-flask conditions the yield was elevated to 91% (entry 2).²⁰ Various other halogenation reagents were examined; as a result, the utility of NCS (**1b**), NIS (**1c**) and selectfluor (**1d**) was proved to be unbeneficial for this reaction and the desired products were afforded in inferior yields (entries 3-5), whereas the NBA (**1e**), NBP (**1f**) and DBDMH (**1g**) resulted in moderate yields of 70%, 75% and 62%, respectively (entries 6-8). An isotope trace experiment employing stoichiometric water (5.0 eq.) labelled with ¹⁸O was performed as predesigned. Diphenylmethane was refluxed with H₂¹⁸O (5.0 equiv) in the presence of NBS (5.0 equiv) in dry CHCl₃ for 3 h in a nitrogen atmosphere; as expected the ¹⁸O-labeled product **3a** confirmed by HRMS was generated in 99% yield (entry 9). This procedure indicates adamantly that the oxygen atom of product originates from the moist surroundings, which is beneficial to the hydrolysis.

Table 1

Optimization of reaction conditions.^a

1a: X = Br (NBS)
1b: X = Cl (NCS)
1c: X = I (NIS)

1d: F-TEADA
1e: NBA
1f: NBP
1g: DBDMH

Entry	Oxidant	Solvent	Yield ^b (%)
1	1a	CHCl ₃	36 ^c
2	1a	CHCl ₃	91
3	1b	CHCl ₃	12
4	1c	CHCl ₃	18
5	1d	CHCl ₃	16
6	1e	CHCl ₃	70
7	1f	CHCl ₃	75
8	1g	CHCl ₃	62
9	1a	CHCl ₃	99 ^d

^a Reaction conditions: diphenylmethane (**2a**, 1.0 mmol), CHCl₃ (4.0 mL), **1a-g** (5.0 mmol), reflux in air for 3 h.

^b Isolated yield.

^c Under nitrogen atmosphere.

^d An isotope trace experiment employing extra 5.0 equiv of water labelled with ¹⁸O.

Having gotten the optimal reaction conditions, an attempt to investigate the scope of the reaction substrates without the addition of water was then conducted (Table 2). Compared with diphenylmethane (entry 1), *para*-chloro substituent **2b** showed higher reactivity affording the desired product in 98% yield (entry 2). Mono-/dihalo substituents **2c** and **2d** were compatible with this procedure and products were isolated in moderate yields (entries 3 and 4). Interestingly, diarylmethanes bearing methoxyl or ethoxyl group at the *para* position on the benzene ring afforded monobromo-substituted ketones **3e** and **3f** in 44% and 66% yields respectively, in which NBS plays a role of dual duty (entries 5 and 6). Differently, 4-benzyltoluene **2g** was converted to two products (**3g¹** and **3g²**) in total yield of 99% (entry 7). Interestingly, when employing 3-bromofluorene as the substrate under the standard reaction conditions, the reaction only afforded the dibrominated product **3h** in 80% yield rather than the corresponding ketone (Scheme 1). We are delighted to have

obtained single crystal structure and confirm it structurally by X-ray diffraction analysis.²¹ It indicated that the halogenation act as a crucial process in this transformation; as a result, selecting diaryl monohalo-methanes **2h-j** as substrates which are regarded as the first monohalogenation intermediates, the reactions proceeded very smoothly. When using half of amount (2.5 equiv) of NBS in standard conditions, the product of **2h** was obtained in 91% yield (Table 2, entry 8). Likewise, excellent yields were provided when employing **2i** and **2j** as the substrates (Table 2, entries 9 and 10).

Table 2

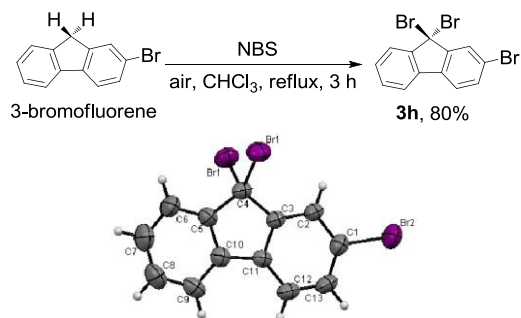
Substrate scope under the moist conditions.^a

Entry	Substrate	Product	Yield ^b (%)
1	2a	3a	91
2	2b	3b	98
3	2c	3c	66
4	2d	3d	44
5	2e	3e	44
6	2f	3f	66
7	2g	3g¹ , R = H 55% 3g² , R = Br 44%	99
8	2h	3a	91 ^c
9	2i	3a	99
10	2j	3b	97

^a Reaction conditions: diarylmethanes (**2a-j**, 1.0 mmol), CHCl₃ (4.0 mL), NBS (5.0 mmol), reflux in air for 3 h.

^b Isolated yield.

^c NBS (2.5 mmol).



Scheme 1. The dibromination of 3-bromofluorene and X-ray structure of **3h**.

The crucial role of moisture to high reactivity and selectivity has been illuminated, which reminded us taking the addition of extra water into consideration, in order to achieve improved substrate generality. We further investigated the scope of halo-substituted substrates, combined with 5.0 equivalents of H₂O under the standard reaction conditions (Table 3). In addition that all of halo-substituents are conveniently functionalized, of special properties, fluoro-containing compounds possess a potential application in modern pharmaceuticals and specialty materials. As a result, the yield of **3d** increased significantly up to 82% (Table 3, entry 9 vs. Table 2, entry 4). Moreover, it was found that when diphenylmethane bearing fluoro, chloro, bromo groups at the *ortho*, *meta* and *para* position were employed as the substrates, the reaction proceeded smoothly affording the desired products in excellent yields of up to 99% (entries 1-6). It is worth to mention that the ketone **3n** has been readily transformed into bioactive 2-(3-benzoylphenoxy)propanamide²² in good yield (see supporting information). Substrates with dihalo-substitution at the different position on the aromatic ring were also suitable under standard conditions to give rise to corresponding diarylketones in good to excellent yields (entries 7-15). In addition, substrates containing a heterocycle thiophene were tested, in which benzylthiophene was converted into two dually functionalized products **3w**¹ and **3w**² in 51% and 38% yields, respectively (entry 16) and 3-(4-fluorobenzyl)thiophene only led to only ketone **3x** in 82% yield when increasing amount of NBS and water (entry 17). It is worth to address that our attempt to decrease the amount of NBS through the usage of stoichiometric water is unsuccessful.

Table 3

Substrate scope in the presence of extra water.^a

Entry	Substrate	Product	Yield ^b (%)
1			97
2			99
3			92
4			91

5			90
6			98
7			99
8			90
9			82
10			99
11			99
12			93
13			99
14			87
15			84
16			51% 89
			38%
17			82 ^c

^a Reaction conditions: diarylmethanes (**2**; 1.0 mmol), CHCl₃ (4.0 mL), NBS (5.0 mmol), H₂O (5.0 mmol), reflux in air for 3 h.

^b Isolated yields.

^c NBS (10.0 mmol), H₂O (10.0 mmol).

In order to gain an insight into the reaction mechanism, a series of control experiments were conducted. As mentioned in Table 1, product **3a** was obtained in a low yield of 36% in a nitrogen atmosphere (Table 1, entry 1). Compared with the reaction providing yield of 4% under the dark conditions, the treatment of **2a** with NBS and H₂O under natural light conditions reacted smoothly to generate **3a** in 97% yield, which implies that the natural light plays a crucial role in this reaction. The process is partially blocked in the presence of the radical scavenger

2,2,6,6-tetramethylpiperidinyloxy (TEMPO), and only the yield of 57% was afforded, which suggested that the reaction precedes a radical process. Based on these control reactions, a plausible reaction mechanism for carbonylation of diarylmethanes is proposed (Figure 1). The initial step of this reaction involves the homolytic cleavage of NBS by both sunlight and reflux to generate free radical Br \cdot . Then abstraction of the benzylic hydrogen atom(s) of diarylmethanes **A** by radical Br \cdot in subsequent steps leads to the di/mono-brominated intermediates **B** and **C**, following hydrolysis and water-elimination of **C** affords the desired ketone **F**. Alternatively, direct hydrolysis of monobrominated product **B** results in the formation of diarylmethanol **D**, which eventually generates the diarylketone **F** under oxidative conditions.

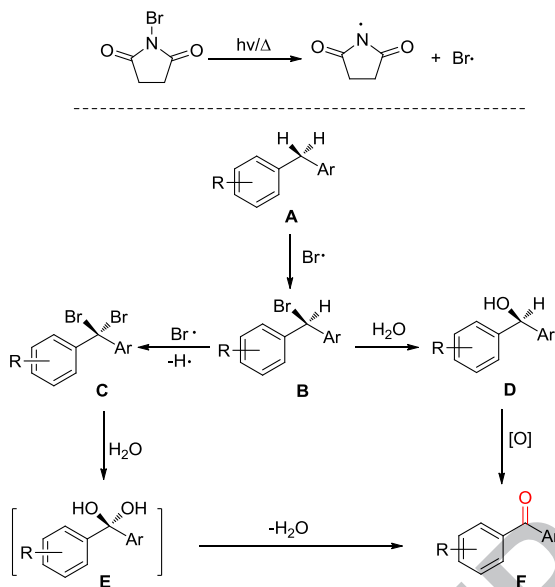


Figure 1. The proposed mechanism.

In conclusion, a highly efficient and convenient method in one-pot to prepare diversely functionalized diarylketones from corresponding diarylmethanes employing commercially available NBS under open-flask conditions has been developed. The isotope trace experiment has proved definitely that water is the true oxygen source and subsequently the addition of stoichiometric water lead to improved yields in all cases. In the control experiments, both the natural light and the heat have proved to be requisite for the initiation of free radical. It should be addressed that the usage amount of NBS is large, however which can be compensated to some extent by commercial availability and low cost of NBS, operational simplicity and high-yielding synthesis.

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Supplementary Material

CCDC 976668 (**3h**) and the data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary data (detailed experimental description, optimization of reaction condition, mechanistic investigations and the route for synthesis of 2-(3-benzoylphenoxy)propanamide,

details of the X-ray analysis, characterization data of NMR and HRMS for all compounds and copies of the ^1H NMR, ^{13}C NMR) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet>.

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20. Typical reaction procedure for the synthesis of **3a**: In a round-bottom flask, diphenylmethane (168.2 mg, 1.0 mmol), NBS (889.9 mg, 5.0 mmol) were dissolved in CHCl_3 (4.0 mL). After refluxing for 3 h in the atmosphere, the reaction mixture was quenched with $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$, cooled to room temperature, washed with 5 mL CH_2Cl_2 , dried with MgSO_4 , and filtered to get clear organic solution. The solvent was removed under vacuum by a rotary evaporator, and the resulting residue was subjected to column chromatography on silica gel to using co-solvent (ethyl acetate/petroleum ether, 1/100) as the eluent to give light yellow liquid **3a** (165.8 mg, 91%). ^1H NMR (500 MHz, CDCl_3) δ 7.79 (d, $J = 7.5$ Hz, 4H), 7.57 (t, $J = 7.5$ Hz, 2H), 7.46 (t, $J = 7.5$ Hz, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.8, 137.7, 132.5, 130.1, 128.4. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{10}\text{O}$ $[\text{M}+\text{H}]^+$ 183.0810, found 183.0808.
21. CCDC 976668 (**3h**) and the data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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