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Triphenylphosphine oxide-catalyzed stereoselective poly- and dibromination of unsaturated compounds†

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A novel PPh_3O catalyzed bromophosphonium salt-mediated dibromination of α,β-unsaturated esters and β,γ-unsaturated α-ketoesters has been developed. The products were obtained with good to excellent yields and excellent diastereoselectivities. This dibromination reaction is a good complement to the field of dibromination.

Organobromine compounds can be found in a variety of natural products (some products are shown in Fig. 1). They are widely used as essential intermediates in the manufacture of derivatives of many natural products, pharmaceuticals, agrochemicals and other fine chemicals.[1] Organobromine compounds are also very useful building blocks for some fundamental chemical transformations such as Grignard reactions, cross-coupling, and nucleophilic substitution, *etc.*

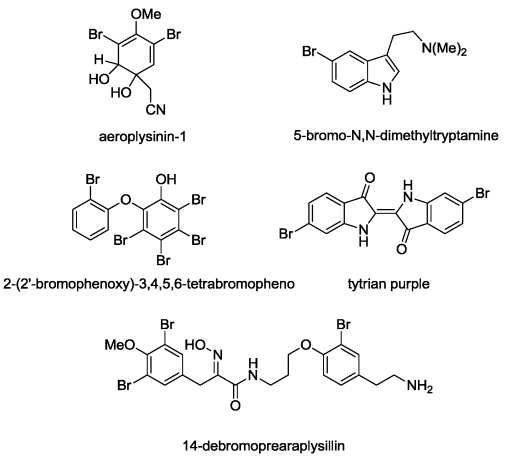

Fig. 1 Some bromine-substituted natural products.

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† Electronic supplementary information (ESI) available: Experimental procedures, analytical data for all compounds, and copies of ^1H and ^{13}C NMR spectra of all the products. CCDC 992325. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc02847c

Therefore, due to the importance of such compounds, bromination of unsaturated C–C bond has attracted considerable attention from the synthetic community. Elemental bromine is frequently used in bromination reactions which, however, usually require harsh conditions.[2] During the past decades, many novel dibromination methods have been developed.[3–5] Among these new alternative methods, the most commonly employed strategies are either to use suitable bromine carrying reagents[3] or to generate bromine *in situ* involving metal catalysts.[4] Despite the significant progress, the use of bromine carrying reagents such as NBS[6] (*N*-bromosuccinimide) and similar compounds will generate a stoichiometric amount of waste which is difficult to dispose and the employment of toxic metal reagents will cause environmental problems. Therefore, it is highly desired to develop safer, more practical and environmentally benign methods to complement the current dibromination research.

It is well known that some reactions, such as Staudinger,[7] Wittig,[8] Mitsunobu[9] and some PPh_3-triggered[10] reactions, usually generate PPh_3O as a waste product. However, the molecular weight of PPh_3O is high (278) which leads to the decreased efficiency of these reactions. Therefore, it is necessary to find a practical method to make use of this waste product and therefore improve the reaction efficiency. Herein, we report our progress toward solving these problems through an efficient triphenylphosphine oxide catalyzed stereoselective dibromination of unsaturated compounds.

To the best of our knowledge, the dibromination reaction using a combination of oxalyl bromide and triphenylphosphine oxide has not been reported before. Based on the results of our previous work (Scheme 1),[11] we envisioned that 1,3-dibromination reaction of unsaturated α-ketoesters might take place if we replace oxalyl chloride with oxalyl bromide. With this idea in mind, we began to investigate this bromination reaction. However, to our surprise, oxalyl chloride and oxalyl bromide showed totally different reactivities and an unexpected dibromination of double bond occurred while the 1,3-dibromination product did not form (Scheme 1).

To generalize the reaction scope, we investigated the reaction by employing the most commonly used unsaturated ester **1a** as a model substrate and oxalyl bromide as a bromine source in the

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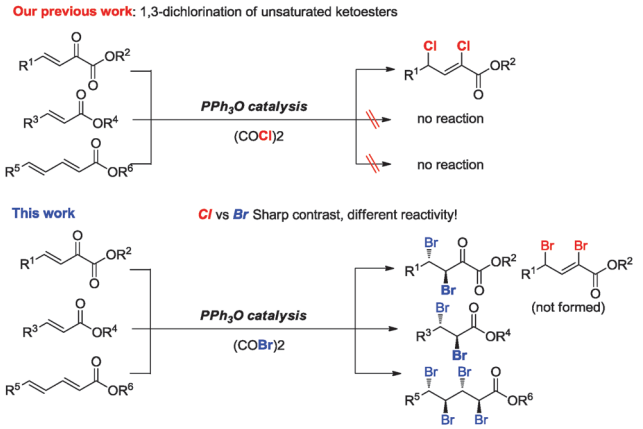


Scheme 1 Dichlorination and dibromination reactions with PPh_3O as the catalyst.

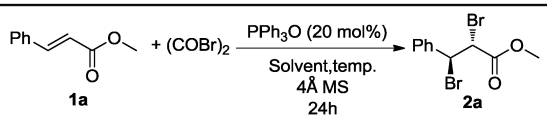
presence of a catalytic amount of PPh_3O (20 mol%) in dry DCE (1,2-dichloroethane) under reflux (Table 1, entry 1). To our delight, the reaction proceeded efficiently to afford the *anti*-selective dibromination product **2a** in excellent yield (92%) with excellent diastereoselectivity (>19 : 1). Then, the reduced amount of oxalyl bromide was tested to determine the effect on the reaction (Table 1, entries 2–4). As expected, the data revealed that a decrease in the amount of oxalyl bromide resulted in a lower yield (Table 1, entries 2–4). Considering that the reaction temperature was relatively high (DCE under reflux), we also performed the reaction at lower temperature (Table 1, entries 5–7). It was observed that nearly the same excellent yields and stereoselectivities were obtained at 60 °C or even at 40 °C (Table 1, entries 5 and 6). However, when the reaction was performed at room temperature, only a trace amount of the product was detected (Table 1, entry 7). Further optimization of the reaction conditions was carried out by screening the reaction solvents. Several solvents such as $CHCl_3$, toluene and THF (Table 1, entries 8–10) were tested, and the results showed that the optimal one was DCE. Moreover, it was notable that only a trace amount of the desired product was detected in the absence of PPh_3O (Table 1, entry 11).

Under the optimal conditions, the scope of the triphenylphosphine oxide catalyzed dibromination reaction was investigated by using various functionalized α,β-unsaturated esters to evaluate the generality of this dibromination reaction.

Generally speaking, as shown in Table 2, the reaction was effective for a broad range of unsaturated esters and provided dibrominated products with good to excellent yields (83–98%) and excellent diastereoselectivities (d.r. > 19 : 1). In all cases, the formation of *anti*-products was preferred. Substrates containing either electron-withdrawing or -donating functional groups in aromatic rings were both tolerated. Meanwhile the substitution position (*ortho*-, *meta*-, and *para*-) of the substituents on aromatic rings had little effect on the reaction efficiency and diastereoselectivity. However, the reaction proceeded faster with substrates containing electron-neutral and donating groups (24 h) than with those containing electron-withdrawing substituents (36 h). Other ester groups were also examined, and it was found that these ester groups could be tolerated in this dibromination reaction (Table 2, entries 13 and 14). Furthermore, we found that both of the aliphatic α,β-unsaturated esters and naphthalenyl α,β-unsaturated ester could work under the reaction conditions and the corresponding dibrominated products were obtained in excellent yields and diastereoselectivities (Table 2, entries 10–12).

Having developed the catalytic dibromination of α,β-unsaturated esters, next, we examined the substrate scope of dibromination reaction of the β,γ-unsaturated α-ketoester (**3**) (Table 3). Again it should be noted that the dibromination of β,γ-unsaturated

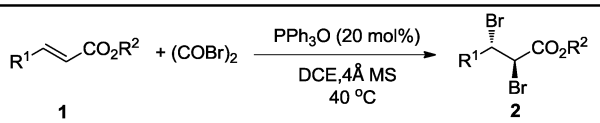
Table 1 Screening of the reaction conditions[a]



Entry	Solvent	*T*	Yield[b] (%)	dr (*anti*/*syn*)[c]
1	DCE	Reflux	92	>19 : 1
2[d]	DCE	Reflux	12	n.d.
3[e]	DCE	Reflux	53	>19 : 1
4[f]	DCE	Reflux	81	>19 : 1
5	DCE	60 °C	90	>19 : 1
6	DCE	40 °C	90	>19 : 1
7	DCE	RT	Trace	n.d.
8	$CHCl_3$	40 °C	80	>19 : 1
9	Toluene	40 °C	61	>19 : 1
10	THF	40 °C	Trace	n.d.
11[g]	DCE	40 °C	Trace	n.d.

[a] Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol, 16.2 mg), oxalyl bromide (29 μL,0.3 mmol), 4 Å MS (40.0 mg), and PPh_3O (20 mol%, 0.02 mmol, 5.6 mg) in the indicated solvent (0.5 mL) for 24 h. [b] Isolated yield after flash chromatography. [c] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [d] 0.1 mmol oxalyl bromide was used. [e] 0.15 mmol oxalyl bromide was used. [f] 0.2 mmol oxalyl bromide was used. [g] Without PPh_3O. n.d. = not determined, MS = molecular sieve.

Table 2 Substrate scope of unsaturated esters[a]



Entry	R^1	R^2	Product	Time (h)	Yield[b] (%)	dr (*anti*/*syn*)[c]
1	2-ClC_6H_4	Me	**2b**	36	91	>19 : 1
2	3-ClC_6H_4	Me	**2c**	36	96	>19 : 1
3	4-ClC_6H_4	Me	**2d**	36	92	>19 : 1
4	4-BrC_6H_4	Me	**2e**	36	92	>19 : 1
5	4-FC_6H_4	Me	**2f**	36	91	>19 : 1
6	2-MeC_6H_4	Me	**2g**	24	92	>19 : 1
7	3-MeC_6H_4	Me	**2h**	24	83	>19 : 1
8	4-MeC_6H_4	Me	**2i**	24	95	>19 : 1
9	4-*t*BuC_6H_4	Me	**2j**	24	95	>19 : 1
10[d]	*n*-Hexanyl	Me	**2k**	24	91	>19 : 1
11[d]	*c*-Hexanyl	Me	**2l**	24	95	11 : 1
12	2-Naphthalenyl	Me	**2m**	36	98	>19 : 1
13	Ph	Et	**2n**	36	88	>19 : 1
14	Ph	Bn	**2o**	36	87	>19 : 1

[a] Unless otherwise noted, the reactions were carried out with **1** (0.1 mmol), oxalyl bromide (0.3 mmol), 4 Å MS (40.0 mg), and PPh_3O (20 mol%, 0.02 mmol, 5.6 mg) in the dry DCE (0.5 mL). [b] Isolated yield after flash chromatography. [c] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [d] Reaction temperature was 60 °C. MS = molecular sieve.

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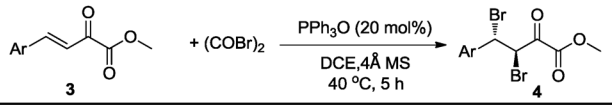
Table 3 Substrate scope of unsaturated ketoesters[a]



Entry	Ar	Product	Yield[b] (%)	dr (*anti*/*syn*)[c]
1	Ph	**4a**	92	8 : 1
2	2-ClC_6H_4	**4b**	81	7 : 1
3	3-ClC_6H_4	**4c**	94	11 : 1
4	4-ClC_6H_4	**4d**	96	9 : 1
5	2-MeC_6H_4	**4e**	82	7 : 1
6	3-MeC_6H_4	**4f**	92	12 : 1
7	4-MeC_6H_4	**4g**	93	9 : 1

[a] Unless otherwise noted, the reactions were carried out with **3** (0.1 mmol), oxalyl bromide (0.3 mmol), 4 Å MS (40.0 mg), and PPh_3O (20 mol%, 0.02 mmol, 5.6 mg) in the dry DCE (0.5 mL) at 40 °C for 5h. [b] The yield was determined by ^1H NMR using 1,1,2,2-tetrachloroethane(TCE) as an internal standard. [c] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. MS = molecular sieve.

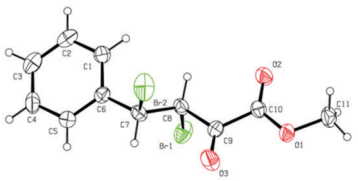
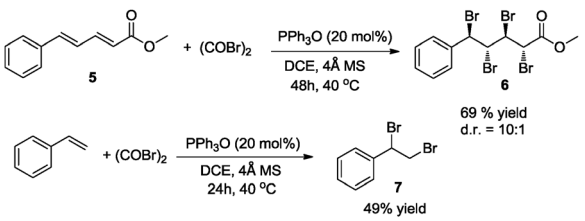


Fig. 2 X-ray crystallographic structure of **4a**.

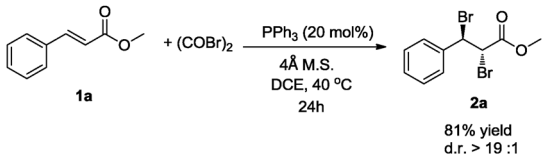
α-ketoester has not been reported before. In general, the β,γ-unsaturated α-ketoester substrates bearing either electron-withdrawing or -donating groups reacted smoothly with oxalyl bromide in the presence of a catalytic amount of PPh_3O to afford the corresponding products in good to excellent yields with excellent diastereoselectivities. The X-ray crystallographic structure of **4a** is shown in Fig. 2.[12] Since products **4a–4g** are not stable, NMR spectroscopic yields were obtained using 1,1,2,2-tetrachloroethane as an internal standard. As a consequence of the steric effect, when substrates bearing *ortho*-substituted groups on aromatic rings were subjected to the reaction, lower yields were observed (Table 3, entries 2 and 5).

To further demonstrate the power of this method, we applied this bromination method to α,β,γ,δ-unsaturated ester **5** and styrene, as shown in Scheme 2, where tetra-brominated compound **6** was obtained in moderate yield with excellent diastereoselectivity, and dibrominated product **7** was obtained in 49% yield.

In order to explore the mechanism of this dibromination reaction, some control experiments were performed. As shown in



Scheme 2 Tetrabromination of compound **5** and dibrominaton of styrene.



Scheme 3 Dibromination reaction catalyzed by PPh_3.

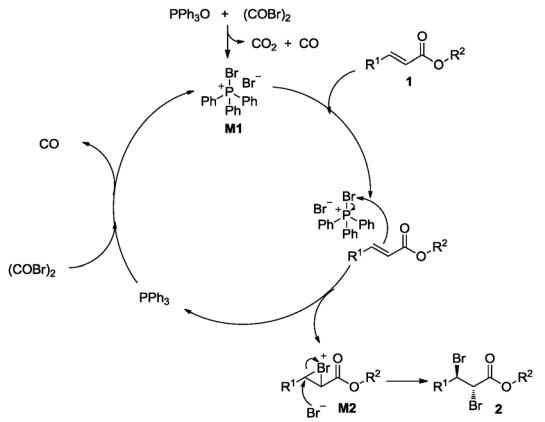


Fig. 3 The proposed mechanism of dibromination reaction.

Scheme 3, it was found that the dibromination reaction could also proceed in the presence of a catalytic amount of PPh_3 (20 mol%).

However, without a catalyst, only a trace amount of conversion was observed. Based on these results described here, a possible mechanism is proposed. As shown in Fig. 3, initially, triphenylphosphine oxide reacts with oxalyl bromide to generate intermediate **M1**,[13] the *in situ* generated bromo-triphenylphosphonium bromide **M1** reacts with unsaturated ester **1** to give a three-membered cyclic bromonium ion intermediate **M2**. The cyclic intermediate then undergoes ring opening reaction by the bromide ion *via* the S_N2 pathway to produce the *anti*-dibrominated product **2** and generate triphenylphosphine (PPh_3). It should be noted that the S_N2 ring-opening is the explanation for high *anti*-stereoselectivity of the product. Finally, PPh_3 reacts with oxalyl bromide to regenerate **M1**.

In conclusion, we have developed a novel bromophosphonium salt-mediated stereoselective dibromination of α,β-unsaturated esters, β,γ-unsaturated α-ketoesters and some other unsaturated compounds. In this reaction, PPh_3O, which is usually considered as the stoichiometric waste product of some common reactions, is employed as a powerful catalyst. A broad substrate scope was observed for this reaction, without specially tailored dibromination reagent, oxalyl bromide can serve as a cheap and commercially available bromine source. Since the byproduct is gas, the desired product can be much easily separated. This methodology also provides a potential route for the synthesis of enantioselective dibrominated products from achiral substrates. The study of the asymmetric dibromination reaction is currently underway in our laboratory.

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