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PPh_3O as an Activating Reagent for One-pot Stereoselective Syntheses of Di- and Poly- brominated Esters from Simple Aldehydes

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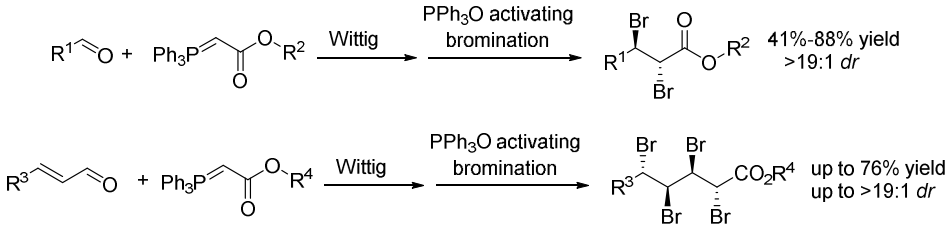


ABSTRACT: An efficient one-pot method for the syntheses of di- and poly-brominated esters from readily available aldehydes is reported. The direct use of the *in situ* generated byproduct PPh_3O in the following reactions greatly improves the efficiency of the cascade. Also, the substrate scope of the reaction is proved to be broad.

INTRODUCTION

During many commonly used reactions, a large amount of waste is

simultaneously produced along with the formation of the desired products.[1] As a result, the waste reduces the synthetic efficiency significantly and then restricts the large scale applications of these reactions. Therefore, one of the fundamental goals for synthetic chemists is to minimize the reaction waste.[2] So far, many elegant methods/strategies have been developed to achieve this goal.[3–4] Among those novel synthetic methods, one of the most efficient ways is to use the *in situ* generated waste as a catalyst or reactant for the following reaction steps.[4] Therefore, this strategy can enable the construction of complex structures from simple starting materials in a one-pot multi-step synthesis which effectively improves the overall efficiency of the cascade reaction.[5]

PPh_3O is often unavoidably generated as a stoichiometric waste in some most commonly used reactions such as Wittig,[6] Mitsunobu,[7] Staudinger[8] and also some PPh_3-triggered reactions.[9] However, the atom efficiency of these reactions is not satisfactory due to the relative high molecular weight of PPh_3O. Meanwhile, in many cases, the separation of desired product will be complicated, which requires a tedious isolation, extra inputs of manpower and materials. To find the solutions to these problems, much effort has been devoted to finding practical usage of the waste products.[10] To improve pot- and step-economy, we envisioned that it would be possible to develop an effective one-pot reaction wherein simple and commercially available starting materials are transformed to the desired substrates, and the waste product, PPh_3O, then acts as an activating reagent in the next step to afford structurally complex products.

Organobromine compounds can often be found in nature products, pharmaceuticals and agrochemicals (Figure 1).[11] Meanwhile, they are also useful building blocks in some fundamental chemical transformations. Therefore, the development of novel bromination methods has attracted considerable attention from synthetic chemists. The employment of molecular bromine, however, has a limited application due to its potentially hazardous risk. During the past years, many innovative bromination methods have been developed, which mainly involved the use of specially tailored bromine carrying reagents and the *in situ* generation of bromine with oxidizing reagents.[12] Despite these significant advances, several problems still remain, which are often associated with the generation of stoichiometric amount of wastes and the employment of toxic metal reagents.

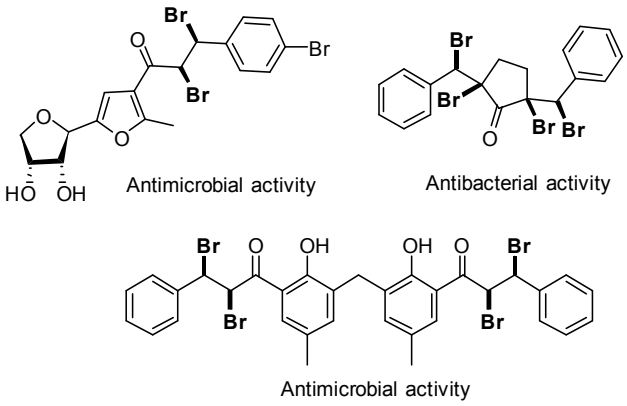


Figure 1. Some bromine-substituted compounds

Recently, our group developed PPh_3O-catalyzed stereoselective halogenation methods.[13] These works have complemented the research in the fields of halogenation and PPh_3O catalysis, however, the pot- and step-economy is still not satisfactory since the preparation of a pure and suitable compound for halogenation is required. In this context, it is highly desirable to develop a more 'ideal' synthesis method, which only

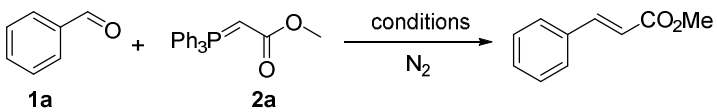
employs simple commercially available reagents to generate reactive intermediates and the byproduct which will then act as an effective activating reagent in the next reaction to afford the desired products in a single operation. Although the same final products will be obtained, the strategies and starting points differ significantly.

Herein, we report the stereoselective syntheses of Di- and Poly-brominated esters by a tandem Wittig/PPh_3O- activated bromination reaction sequence using commercially available aldehydes as the starting materials.

RESULTS AND DISCUSSION

Initially, the most commonly used benzaldehyde (**1a**) and phosphorus ylide **2a** were employed as the model substrates to test our design. The reaction was carried out in DCE at room temperature. Oxalyl bromide was added upon the complete consumption of the aldehyde. After 24h, dibrominated ester **3a** was obtained in 73% yield and >19:1 dr. Encouraged by this positive result, we began to optimize this cascade reaction. First, after careful screening of temperature, amount of **2a** and the solvent (Table 1), the optimal reaction conditions for the synthesis of unsaturated ester were found to be the use of aldehyde **1a** and 1.2 equivalent of phosphorus ylide **2a** at room temperature in DCE.

Table 1. Optimization of Wittig reaction[a]



1a **2a**

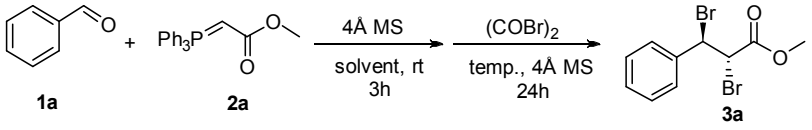
Entry	Solvent	*Temp.*	Time (h)	Yield (%)[b]	*E/Z*[c]
1	DCE	rt	3	86	>19 : 1
2[d]	DCE	rt	3	86	>19 : 1
3	DCE	40 °C	3	86	>19 : 1
4	DCE	rt	2	80	>19 : 1

5	DCE	rt	4	86	>19 : 1
6	CH_3CN	rt	3	83	>19 : 1
7	$CHCl_3$	rt	3	77	>19 : 1
8	toluene	rt	3	74	>19 : 1

[a] Unless otherwise noted, the reactions were carried out with **1a** (0.2 mmol), **2a** (0.24 mmol) and 4Å MS (40.0 mg) in the indicated solvent (0.5 mL). [b] Isolated yield after flash chromatography. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] 0.3 mmol **2a** was used.

Then, we optimized this one-pot tandem reaction which produced dibrominated ester **3a** from simple aldehyde **1a** and ylide **2a** (Table 2). Different reaction temperatures were tested to determine the effect on the reaction (Table 2, entries 1−3). As shown in Table 2, the data revealed that 40°C was the best temperature for the second step. Then the amount of oxalyl bromide was investigated and 3.0 equiv. was found to be optimal. Finally, several solvents ($CHCl_3$, CH_3CN, toluene and THF) were evaluated (Table 2, entries 6−9) and DCE was proved to be the most promising one.

Table 2. Optimization of one-pot dibromination reaction[a]



1a 2a 3a

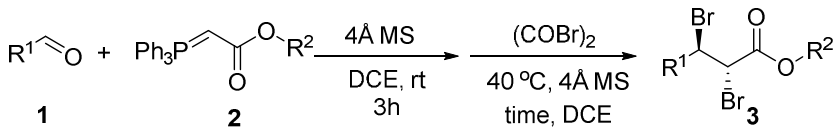
entry	solvent	Temp.	Yield (%)[b]	dr (*anti/syn*)[c]
1	DCE	rt	73	>19 : 1
2	DCE	40 °C	85	>19: 1
3	DCE	60 °C	59	>19 : 1
4[d]	DCE	40 °C	30	>19 : 1
5[e]	DCE	40 °C	85	>19 : 1
6	$CHCl_3$	40 °C	53	>19 : 1
7	CH_3CN	40 °C	51	>19 : 1

8	toluene	40 °C	47	>19 : 1
9	THF	40 °C	trace	n.d.

[a] Unless otherwise noted, the reactions were carried out with **1a** (0.2 mmol), **2a** (0.24 mmol) and 4Å MS (40.0 mg) in the indicated solvent (0.5 mL) at rt for 3h, followed by the addition of oxalyl bromide (0.6 mmol) and stirring at indicated temperature for 24h. [b] Isolated yield after flash chromatography. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] 0.4 mmol oxalyl bromide was used. [e] 0.8 mmol oxalyl bromide was used. n.d. = not determined, MS = molecular sieve.

With optimal conditions in hand, the substrate scope of the reaction was then investigated (Table 3). A variety of functionalized aromatic and aliphatic aldehydes were employed to evaluate the generality of this one-pot reaction. As shown in Table 3, in all cases, the reaction proceeded smoothly to produce the anti-dibrominated[13b] ester **3** with moderate to good yields (41%−88%) and excellent diastereoselectivities (d.r.>19:1). The results demonstrated that no alpha-epimerization took place under the reaction conditions. The substitution position (ortho-, meta-, and para-) of the substituents on aromatic ring had little influence on the results (Table 3, entries 2−4, 10−12). Both of the electron-withdrawing and electron–donating functional groups in aromatic ring were tolerated in this reaction, although the substrates containing electron-neutral and electron-donating substituents proceeded faster than those containing electron-withdrawing substituents. The aliphatic substrate also worked well and the product was obtained with excellent dr and moderate yield (Table 3, entry 15−16). Another phosphorus ylide was found to work well with **1a**, which afforded **3q** in good yield with excellent diastereoselectivity (Table 3, entry 17).

Table 3. Substrate scope of one-pot dibromination reaction.[a]



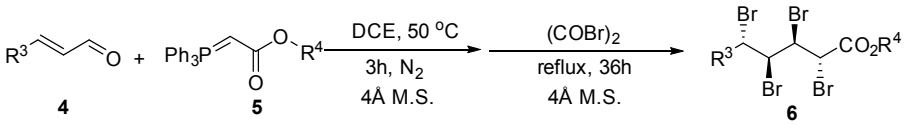
Entry	R^1	R^2	Product	Time (h)	Yield (%)[b]	dr (*anti/syn*)[c]
1	Ph	Me	**3a**	24	85	>19 : 1
2	2-ClC_6H_4	Me	**3b**	36	80	>19: 1
3	3-ClC_6H_4	Me	**3c**	36	77	>19 : 1
4	4-ClC_6H_4	Me	**3d**	36	80	>19 : 1
5	3,4-$Cl_2C_6H_3$	Me	**3e**	36	88	>19 : 1
6	4-BrC_6H_4	Me	**3f**	36	85	>19 : 1
7	4-FC_6H_4	Me	**3g**	36	75	>19 : 1
8	4-$NO_2C_6H_4$	Me	**3h**	36	69	>19 : 1
9	4-CNC_6H_4	Me	**3i**	36	66	>19 : 1
10	2-MeC_6H_4	Me	**3j**	24	70	>19 : 1
11	3-MeC_6H_4	Me	**3k**	24	74	>19 : 1
12	4-MeC_6H_4	Me	**3l**	24	67	>19 : 1
13	3,4-$Me_2C_6H_3$	Me	**3m**	24	56	>19 : 1
14	4-*t*BuC_6H_4	Me	**3n**	24	74	>19 : 1
15[d]	*n*-hexyl	Me	**3o**	24	66	>19 : 1
16[d]	*i*-propyl	Me	**3p**	24	42	>19 : 1
17	Ph	Et	**3q**	24	83	>19 : 1

[a] Unless otherwise noted, the reactions were carried out with **1** (0.2 mmol), **2** (0.24 mmol) and 4Å MS (40.0 mg) in dry DCE (0.5 mL) at rt for 3h, followed by the addition of oxalyl bromide (0.6 mmol) and stirring at 40 °C. [b] Isolated yield after flash chromatography. [c] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [d] The reaction temperature of second step is 60 °C. MS= molecular sieve.

To further demonstrate the synthetic value of this one-pot bromination method, we decided to explore the utilization of this bromination reaction in the syntheses of poly-brominated molecules. Therefore, we applied this method to the reaction of *α,β*-unsaturated aldehyde **4** and ylide **5**, which proceeded smoothly to produce the desired poly-brominated product. After reaction condition optimization (see the

Supporting Information), the substrate scope of this one-pot poly-bromination reaction was established. As shown in Table 4, this method was applicable to a wide range of *α,β*-unsaturated aldehydes with different aryl substituents. In general, moderate to good yields and good diastereoselectivities were attainable for the examples examined. As a consequence of different reactivities in Wittig step, substrates bearing electron-withdrawing groups had higher yields than those bearing electron-neutral and electron-donating groups. Then, we investigated the effect of substituent position on the reaction yield and diastereoselectivity (Table 4, entries 2−4). As the data revealed, *meta*-substituted substrate had best yield and diastereoselectivity due to a synergistic effect of inductive effect and steric effect (Table 4, entry 3). We also observed an increase in yield but a decrease in diastereoselectivity as a result of substituent's inductive effect (−F > −Cl > −Br) (Table 4, entries 4, 6−7). Meanwhile, disubstituted aldehyde (disubstitution is on the aromatic portion) also worked well under the optimized reaction conditions, both of the yield and diastereoselectivity were satisfactory (Table 4, entry 5). Finally, we tested another phosphorus ylide and the reaction proceeded smoothly to provide the desired product **6i** (Table 4, entry 9). The X-ray crystallographic structure of **6a** was shown in Figure 2.[14] The relative configuration of this product (**6a**) described in our previous paper[13*b*] is misassigned and should be corrected accordingly and the relative stereochemistry in the minor tetrabromide diastereomer is unknown yet.

Table 4. Substrate scope of one-pot tetra-bromination reaction.[a]



4 5 6

Entry	R^3	R^4	Product	Yield (%)[b]	dr [c]
1	Ph	Me	**6a**	58	13 : 1
2	2-ClC_6H_4	Me	**6b**	70	7 : 1
3	3-ClC_6H_4	Me	**6c**	76	>19 : 1
4	4-ClC_6H_4	Me	**6d**	67	15 : 1
5	3,5-$Cl_2C_6H_3$	Me	**6e**	74	11 : 1
6	4-BrC_6H_4	Me	**6f**	70	13 : 1
7	4-FC_6H_4	Me	**6g**	58	>19 : 1
8	4-MeC_6H_4	Me	**6h**	20	4 : 1
9	Ph	Et	**6i**	58	11 : 1

[a] Unless otherwise noted, the reactions were carried out with **4** (0.2 mmol), **5** (0.24 mmol) and 4Å MS (40.0 mg) in dry DCE (0.5 mL) at 50 °C for 3h, followed by the addition of oxalyl bromide (1.0 mmol) and stirring under reflux condition for 36h. [b] Isolated yield after flash chromatography. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. MS= molecular sieve.

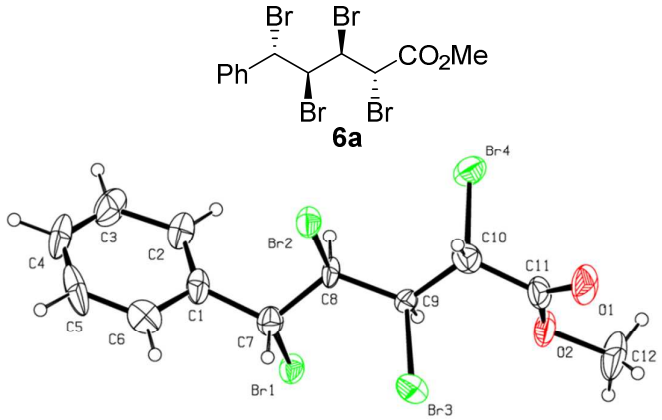


Figure 2. X-ray crystallographic structure of **6a**

To extend the substrate scope of the reaction, we also used this bromination

method to produce dibrominated ketone and cyclic compound. As shown in Figure 3, 2,3-dibromo-1,3-diphenylpropan-1-one (**8**) was produced in 22% yield and 8:1 d,r, and the yield of dibrominated product **10** is 9%.

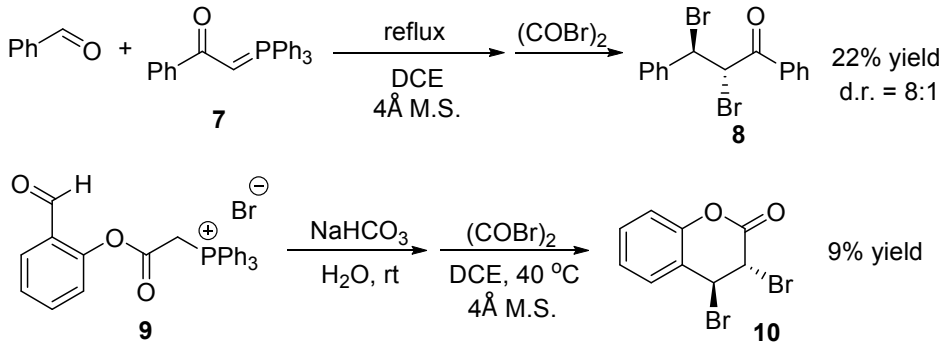


Figure 3 Two applications of the bromination method.

To further investigate the reaction mechanism, methyl (*Z*)-3-phenylacrylate[17] was employed in this dibromination reaction, compared with methyl (*E*)-3-phenylacrylate[13b], it was found that both of the yield and dr decreased (Figure 4), which was believed to be caused by steric hinderance effect. Two substituents which are originally at the same side of the double bond will be an obstacle to the bromide ion attacking on the three-membered cyclic bromonium ion intermediate[20]. On the basis of our previous related study[13] and the data observed, a possible reaction mechanism is proposed. As shown in Figure 5, initially, aldehyde reacts with phosphorus ylide to afford unsaturated ester and triphenylphosphine oxide (Wittig reaction). Next, oxalyl bromide is added to the mixture and reacts with triphenylphosphine oxide to produce **M1**. Bromotriphenylphosphonium bromide (**M1)** reacts with the unsaturated ester, which is produced in former Wittig reaction, to generate a three-membered cyclic bromonium ion intermediate **M2**. Finally, **M2** is

attacked by bromide ion via S_N2 path way to form dibrominated product.

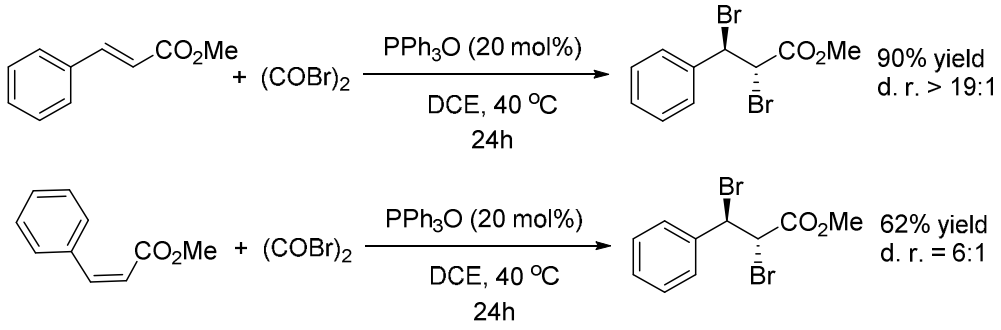


Figure 4. Two dibromination reactions.

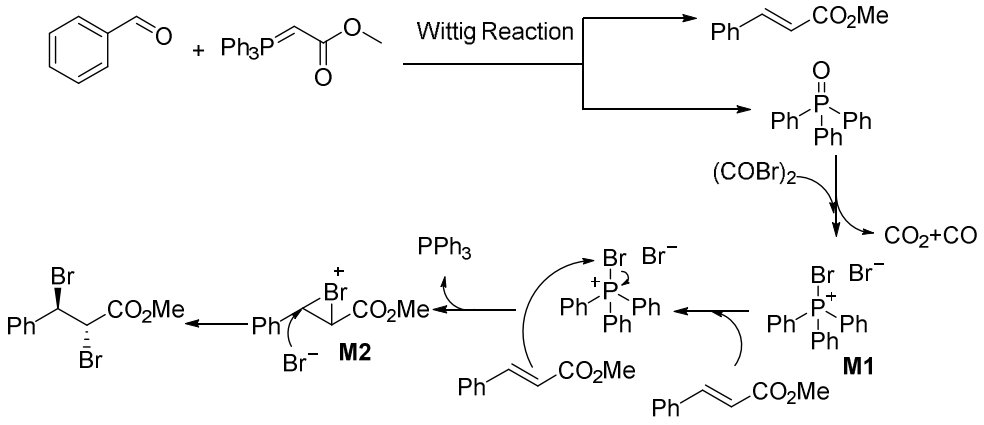


Figure 5. Proposed mechanism of the one-pot reaction.

CONCLUSIONS

In summary, by using easily available reagents as starting materials, we have successfully developed a practical tandem one-pot Wittig/bromination reaction procedure which efficiently produces di- and poly-brominated esters with satisfactory yields, diastereoselectivties and broad substrate scope. Ph_3PO, which is the by-product in Wittig reaction, directly serves as the activating reagent for the next bromination reaction, which results in a great improvement in the efficiency of this reaction. Considering that PPh_3O is usually generated as the waste product in many reactions, it should not be surprising that this general strategy can be applied to a

variety of such reactions thus to improve the efficiencies of these reactions.

EXPERIMENTAL SECTION

General Information. Chemicals and solvents were either purchased from commercial suppliers or purified by standard procedures as specified in *Purification of Laboratory Chemicals*, 4th Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator and compounds were visualized by irradiation with UV light. Flash column chromatography was carried out using silica gel (200–300 mesh) at increased pressure. The NMR spectra were recorded in $CDCl_3$ as the solvent at room temperature (400 MHz ^{1}H, 100 MHz ^{13}C). ^{1}H and ^{13}C chemical shifts are reported in ppm relative to either the residual solvent peak (^{13}C) or TMS (^{1}H) as an internal standard. IR spectra were recorded using FT-IR instrument. HRMS were performed on ORBITRAP ELITE instrument (ESI). The unsaturated aldehyde substrates were prepared according to the literature procedures.[15]

General Procedure for the Preparation of Compounds 3a−3q. Aldehyde **1** (0.20 mmol), Ylide **2** (0.24 mmol) and 4Å molecular sieve (40.0 mg) were added to a flame-dried Schlenk tube. The vessel was placed under vacuum and the atmosphere was exchanged with N_2 three times before dry DCE (0.5 ml) was added. The mixture was stirred at room temperature for 3h. Then, oxalyl bromide (0.6 mmol) was added to the stirred reaction mixture. The final reaction mixture was stirred at 40 ^{o}C for 24h or 36h. After the reaction was complete, the reaction mixture was purified by flash column chromatography using petroleum ether/EtOAc (80:1) to obtain the desired

product **3**.

(*trans*)-methyl 2,3-dibromo-3-phenylpropanoate (3a). A white solid (55 mg, 85%, d.r. > 19:1), m.p. 109−110 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.85 (d, *J* = 11.6 Hz, 1H), 5.34 (d, *J* = 12.0 Hz, 1H), 7.36−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 137.5, 129.4, 128.9, 128.0, 53.4, 50.6, 46.7; IR (KBr): 3460, 3347, 3010, 1738, 1434, 1380, 1274, 1220, 1152, 700, 587cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{10}Br_2NaO_2$) requires *m/z* 342.8940*,* found *m/z* 342.8949.

(*trans*)-methyl 2,3 -dibromo-3-(2-chlorophenyl) propanoate (3b). A white solid (57 mg, 80%, d.r. > 19:1), m.p. 80−81 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.94 (s, 1H), 5.91 (s, 1H), 7.27−7.36 (m, 2H), 7.40−7.42 (m, 1H), 7.46−7.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 135.1, 134.0, 130.3, 130.2, 128.9, 127.6, 53.5, 45.4; IR (KBr): 3351, 3016, 2954, 2921, 2377, 1745, 1593, 1435, 1377, 1273, 1151, 1038, 763, 736, 605, 575 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_9Br_2ClNaO_2$) requires *m/z* 376.8550 *,* found *m/z* 376.8560.

(*trans*)-methyl 2,3-dibromo-3-(3-chlorophenyl)propanoate (3c). A white solid (55mg, 77%, d.r. > 19:1), m.p. 63−64 ^{o}C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.78 (d, *J* = 12.0 Hz, 1H), 5.28 (d, *J* = 11.6 Hz, 1H), 7.27−7.35 (m, 3H), 7.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 139.5, 134.7, 130.1, 129.6, 128.2, 126.3, 53.5, 49.2, 46.3; IR (KBr): 3473, 3007, 2953, 1748, 1596, 1576, 1478, 1435, 1377, 1302, 1268, 1149, 790, 700, 610, 573 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_9Br_2ClNaO_2$) requires *m/z* 376.8550 *,* found *m/z* 376.8556.

(*trans*)-methyl2,3-dibromo-3-(4-chlorophenyl)propanoate (3d). A white solid (57

mg, 80%, d.r. > 19:1), m.p. 96−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 4.79 (d, *J* = 11.6 Hz, 1H), 5.31 (d, *J* = 12.0 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 136.1, 135.2, 129.4, 129.2, 53.5, 49.5, 46.5; IR (KBr): 3460, 3012, 2957, 1742, 1594, 1742, 1594, 1493, 1435, 1377, 1277, 1231, 1146, 1088, 982, 835, 735, 587 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_9Br_2ClNaO_2$) requires *m/z* 376.8550 , found *m/z* 376.8557.

(*trans*)-methyl 2,3-dibromo-3-(3,4-dichlorophenyl) propanoate (3e). A white solid (69 mg, 88%, d.r. > 19:1), m.p. 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.75 (d, *J* = 11.6 Hz, 1H), 5.26 (d, *J* = 11.6 Hz, 1H), 7.24 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 137.7, 133.6, 133.1, 130.9, 130.1, 127.3, 53.6, 48.4, 46.1; IR (KBr): 3008, 2954, 1748, 1563, 1473, 1405, 1364, 1298, 1267, 1216, 1144, 1032, 883, 823, 739, 600, 475 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_8Br_2Cl_2NaO_2$) requires *m/z* 410.8160, found *m/z* 410.8171.

(*trans*)-methyl 2,3-dibromo-3-(4-bromophenyl) propanoate (3f). A white solid (68 mg, 85%, d.r. > 19:1), , m.p. 106−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 4.78 (d, *J* = 12.0 Hz, 1H), 5.30 (d, *J* = 12.0 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 136.6, 132.1, 129.6, 123.4, 53.5, 49.5, 46.4; IR (KBr): 3454, 3009, 2376, 1747, 1590, 1378, 1279, 1148, 1073, 1011, 827, 583 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_9Br_3NaO_2$) requires *m/z* 420.8045, found *m/z* 420.8051.

(*trans*)-methyl 2,3-dibromo-3-(4-fluorophenyl)propanoate (3g). A white solid (51 mg, 75%, d.r. > 19:1), m.p. 63−64 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.79 (d, *J* = 12.0 Hz, 1H), 5.33 (d, *J* = 12.0 Hz, 1H),7.08 (t, *J* = 8.8 Hz, 2H), 7.37-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 163.0 (d, *J* = 248 Hz), 133.6 (d, *J* = 10 Hz), 130.0 (d, *J* = 10 Hz), 116.0 (d, *J* = 20 Hz), 53.5, 49.7, 46.8; IR (KBr): 3461, 3011, 2953, 1893, 1751, 1604, 1512, 1437, 1378, 1225, 985, 857, 592, 512 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_9Br_2FNaO_2$) requires *m/z* 360.8846 , found *m/z* 360.8851.

(*trans*)-methyl 2,3-dibromo-3-(4-nitrophenyl)propanoate (3h): A white solid (51 mg, 69%, d.r. > 19:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 4.81 (d, *J* = 12.0 Hz, 1H), 5.40 (d, *J* = 11.6 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 8.27 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 148.1, 144.4, 129.2, 124.1, 53.7, 48.0, 45.7 HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{10}Br_2NO_4$) requires *m/z* 365.8971 , found *m/z* 365.8977.

(*trans*)-methyl 2,3-dibromo-3-(4-cyanophenyl)propanoate (3i): A white solid (46 mg, 66% yield, d.r. > 19:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.79 (d, *J* = 11.6 Hz, 1H), 5.34 (d, *J* = 12.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 142.5, 132.7, 128.9, 118.0, 113.2, 53.6, 48.5, 45.7; HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{10}Br_2NO_2$) requires *m/z* 345.9073 , found *m/z* 345.9076.

(*trans*)-methyl 2,3-dibromo-3-(o-tolyl)propanoate (3j). A white solid (47mg, 70%, d.r. > 19:1), m.p. 83−84 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.90 (s, 3H),

4.93 (d, J = 11.6 Hz, 1H), 5.64 (d, J = 12.0 Hz, 1H), 7.17−7.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 136.5, 135.7, 130.8, 129.1, 126.9, 126.8, 53.4, 46.2, 19.4; IR (KBr): 3456, 3023， 2952， 1745， 1436， 1377， 1271， 1150， 983， 769， 726， 604， 497 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{12}Br_2NaO_2$) requires *m/z* 356.9096, found *m/z* 356.9101.

***(trans*)-methyl 2,3-dibromo-3-(m-tolyl)propanoate (3k)**. A white solid (50 mg, 74%, d.r. >19:1), m.p. 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.89 (s, 3H), 4.84 (d, J = 11.6 Hz, 1H), 5.31 (d, J = 11.6 Hz, 1H), 7.15−7.20 (m, 3H), 7.25−7.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 138.7, 137.4, 130.2, 128.7, 128.6, 125.1, 53.4, 50.8, 46.7, 21.4; IR (KBr): 3089, 2921, 2392, 1747, 1436, 1377, 1273, 1145, 1019, 983, 700, 611 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{12}Br_2NaO_2$) requires *m/z* 356.9096, found *m/z* 356.9102.

(*trans*)-methyl 2,3-dibromo-3-(p-tolyl)propanoate (3l). A white solid (45 mg, 67%, d.r. > 19:1), m.p. 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.89 (s, 3H), 4.84 (d, J = 11.6 Hz, 1H), 5.33 (d, J = 12.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 139.5, 134.6, 129.6, 127.9, 53.4, 50.8, 46.8, 21.3; IR (KBr): 3472, 3008, 1911, 1746, 1437, 1268, 1146, 1012, 740, 590, 516 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{12}Br_2NaO_2$) requires *m/z* 356.9096, found *m/z* 356.9101.

(*trans*)-methyl 2,3-dibromo-3-(3,4-dimethylphenyl) propanoate (3m). A white solid (39 mg, 56%, d.r. > 19:1), m.p. 121−122 °C; ^{1}H NMR(400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.28 (s, 3H), 3.89 (s, 3H), 4.85 (d, J = 12.0 Hz, 1H), 5.31 (d, J = 12.0 Hz, 1H),

7.11−7.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 138.2, 137.3, 134.9, 130.1, 129.1, 125.4, 53.4, 51.0, 46.8, 19.8, 19.6; IR (KBr): 3477, 3010, 2972, 2920, 1748, 1505, 1432, 1377, 1267, 1143, 740, 701, 663, 608, 541 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{14}Br_2NaO_2$) requires *m/z* 370.9253, found *m/z* 370.9259.

(*trans*)-methyl 2,3-dibromo-3-(4-(tert-butyl)phenyl) propanoate (3n). A white solid (56 mg, 74%, d.r. > 19:1), m.p. 104−105 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 3.89 (s, 3H), 4.86 (d, *J* = 12.0 Hz, 1H), 5.35 (d, *J* = 12.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 152.6, 134.4, 127.7, 125.8, 53.4, 50.8, 46.8, 34.7, 31.2; IR (KBr): 3476, 3002, 2964, 1916, 1748, 1609, 1436, 1269, 1145, 1020, 835, 739, 590, 499 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}Br_2NaO_2$) requires *m/z* 398.9566, found *m/z* 398.9570.

(*trans*)-methyl 2,3-dibromononanoate (3o). A colorless oil (30 mg, 45%, d.r. > 19:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.32−1.39 (m, 6H), 1.46−1.49 (m, 1H), 1.56−1.59 (m, 1H), 1.77−1.86 (m, 1H), 2.20−2.28 (m, 1H), 3.83 (s, 3H), 4.34−4.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 53.2, 52.8, 47.7, 35.1, 31.5, 28.4, 26.2, 22.5, 14.0; IR (KBr): 3001, 2955, 2929, 2858, 1753, 1437, 1378, 1268, 1150, 1023, 720, 565 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{18}Br_2NaO_2$) requires *m/z* 350.9566 , found *m/z* 350.9572.

(*trans*)-methyl 2,3-dibromo-4-methylpentanoate (3p)[16] : A colorless oil (24mg, 42%, d.r. > 19:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, J = 6.8 Hz, 3H), 1.09 (d, J

= 6.8 Hz, 3H), 2.35 (m, 1H), 3.84 (s, 3H), 4.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 61.3, 53.2, 46.1, 29.4, 22.0, 15.1;

(*trans*)-ethyl 2,3-dibromo-3-phenylpropanoate (3q). A colorless solid (56 mg, 83%, d.r. > 19:1), m.p.73−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.2 Hz, 3H), 4.35 (q, *J* = 6.8 Hz, 2H), 4.83 (d, *J* = 11.6 Hz, 1H), 5.34 (d, *J* = 12.0 Hz, 1H), 7.35−7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 137.6, 129.3, 128.9, 128.0, 62.6, 50.7, 47.0, 13.9; IR (KBr): 3453, 3011, 2986, 1741, 1456, 1379, 1272, 1148, 1026, 697, 602, 562 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{12}Br_2NaO_2$) requires *m/z* 356.9096, found *m/z* 356.9100.

General Procedure for the Preparation of Compounds 6a−6i. Unsaturated aldehyde **4** (0.20 mmol), Ylide **5** (0.24 mmol) and 4Å molecular sieve (40.0 mg) were added to a flame-dried Schlenk tube. The vessel was placed under vacuum and the atmosphere was exchanged with N_2 three times before dry DCE (0.5 ml) was added. The mixture was stirred at 50 °C for 3h. Then, oxalyl bromide (1.0 mmol) was added to the stirred reaction mixture. The final reaction mixture was stirred under reflux condition for 36h. After the reaction was complete, the reaction mixture was purified by flash column chromatography using petroleum ether/EtOAc (100:1) to obtain the desired product **6**.

Compound 6a. A white solid (59 mg, 58%, d.r. = 13:1), m.p. 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.72 (d, *J* = 11.2 Hz, 1H), 5.06 (dd, *J* = 11.2Hz, 2.0 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 5.31 (dd, *J* = 11.0 Hz, 1.6 Hz, 1H), 7.34−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 139.0, 129.2, 128.9, 128.1, 57.0, 55.0,

54.7, 53.6, 47.2; IR (KBr): 3338, 3001, 2952, 2925, 2372, 1748, 1592, 1433, 1382, 1265, 1142, 1021, 690, 601, 576 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}Br_4NaO_2$) requires *m/z* 526.7463, found *m/z* 526.7471.

Compound 6b. A white solid (76 mg, 70%, d.r. = 7:1), m.p. 100−102 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 4.72 (d, *J* = 11.2 Hz, 1H), 5.06 (dd, *J* = 11.2 Hz, 2.0 Hz, 1H), 5.29 (dd, *J* = 11.2 Hz, 1.6 Hz, 1H), 5.94 (d, *J* = 11.2 Hz, 1H), 7.26−7.31 (m, 1H), 7.34−7.41 (m, 2H), 7.56−7.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 136.8, 133.6, 130.1, 129.8, 129.1, 127.7, 56.3, 54.2, 53.6, 49.3, 47.2; IR (KBr): 3478, 3007, 2954, 1748, 1478, 1437, 1276, 1147, 1039, 983, 734, 611, 581, 457 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$($C_{12}H_{11}Br_4ClNaO_2$) reqiures *m/z* 560.7073, found *m/z* 560.7086.

Compound 6c. A white solid (82 mg, 76%, d.r. > 19:1), m.p. 96−97 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.98 (dd, *J* = 11.2 Hz, 2.0 Hz, 1H), 5.17 (d, *J* = 11.2 Hz, 1H), 5.27 (dd, *J* = 11.2 Hz, 2.0 Hz, 1H), 7.28−7.34 (m, 3H), 7.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 140.9, 134.6, 130.1, 129.4, 128.3, 126.4, 56.6, 54.4, 53.7, 53.6, 47.1; IR (KBr): 3479, 3006, 2954, 1749, 1595, 1576, 1476, 1435, 1273, 1146, 1022, 895, 739, 693, 582 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{11}Br_4ClNaO_2$) reqiures *m/z* 560.7073, found *m/z* 560.7084.

Compound 6d. A white solid (73 mg, 67%, d.r. = 15:1), m.p.141−142 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.99 (dd, *J* = 10.8 Hz, 1.6 Hz, 1H), 5.20 (d, *J* = 11.2 Hz, 1H), 5.28 (dd, *J* = 10.8 Hz, 1.6 Hz, 1H), 7.35 (d, *J* =

9.6 Hz, 2H), 7.37 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 137.6, 135.0, 129.5, 129.1, 56.8, 54.5, 53.9, 53.6, 47.1; IR (KBr): 3473, 2953, 1746, 1595, 1491, 1437, 1413, 1267, 1084, 1022, 831, 741, 602, 576, 533, 410 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{11}Br_4ClNaO_2$) reqiures *m/z* 560.7073, found *m/z* 560.7087.

Compound 6e. A white solid (85 mg, 74%, d.r. = 11:1), m.p. 150−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 4.69 (d, *J* = 11.2 Hz, 1H), 4.92 (dd, *J* = 11.2 Hz, 1.6 Hz, 1H), 5.11 (d, *J* = 11.2 Hz, 1H), 5.23 (dd, *J* = 11.2 Hz, 1.6 Hz, 1H), 7.29−7.30 (m, 2H), 7.34−7.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 142.1, 135.3, 129.4, 126.8, 56.3, 54.1, 53.6, 52.7, 46.9; IR (KBr): 3481, 3080, 2953, 1750, 1572, 1435, 1278, 1204, 1146, 1023, 860, 804, 741, 691, 585, 542 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$($C_{12}H_{10}Br_4Cl_2NaO_2$) reqiures *m/z* 594.6684, found *m/z* 594.6694.

Compound 6f. A white solid (82 mg, 70%, d. r. = 13:1), m.p.153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.99 (dd, *J* = 11.0 Hz, 2.0 Hz, 1H), 5.18 (d, *J* = 11.2 Hz, 1H), 5.27 (dd, *J* = 10.8 Hz, 1.6 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 138.1, 132.1, 129.8, 123.2, 56.7, 54.4, 54.0, 53.6, 47.1; IR (KBr): 3348, 2997, 2951, 2371, 1747, 1589, 1486, 1436, 1379, 1264, 1146, 1070, 1022, 827, 741, 603, 524 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$($C_{12}H_{11}Br_5NaO_2$) requires *m/z* 604.6568, found *m/z* 604.6578.

Compound 6g. A white solid (61 mg, 58%, d.r. > 19:1), m.p.112−113 °C; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.71 (d, *J* = 11.2 Hz, 1H), 5.00 (dd, *J* = 11.0 Hz, 1.8 Hz, 1H), 5.22 (d, *J* = 11.2 Hz, 1H), 5.29 (dd, *J* = 10.8 Hz, 2.0 Hz, 1H), 7.08 (t, *J* = 8.4 Hz, 2H), 7.38−7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 162.8 (d, *J* = 250 Hz), 135.1 (d, *J* = 3 Hz), 130.0 (d, *J* = 8 Hz), 115.9 (d, *J* = 22 Hz), 57.2, 54.6, 54.1, 53.6, 47.2; IR (KBr): 3480, 3005, 2955, 2848, 1749, 1604, 1511, 1437, 1275, 1232, 1146, 1018, 838, 740, 607, 630, 468 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$($C_{12}H_{11}Br_4FNaO_2$) requires *m/z* 544.7369, found *m/z* 544.7375.

Compound 6h. A white solid (21 mg, 20%, d.r.=4:1), m.p. 89−90 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.88 (s, 3H), 4.72 (d, *J* = 11.2 Hz, 1H), 5.05 (dd, *J* = 10.8 Hz, 1.6 Hz, 1H), 5.22 (d, *J* = 11.2 Hz, 1H), 5.31 (dd, *J* = 11.0 Hz, 1.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 139.4, 136.2, 129.6, 128.0, 57.2, 55.2, 54.8, 53.6, 47.3, 21.3; IR (KBr): 3005, 2953, 1750, 1593, 1436, 1380, 1273, 1146, 1022, 819, 768, 723, 606, 578 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$($C_{13}H_{14}Br_4NaO_2$) requires *m/z* 540.7620, found *m/z* 540.7626.

Compound 6i. A white solid (61 mg, 58%, d.r. = 11:1), m.p. 100−101 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3H), 4.34 (qd, *J* = 7.0 Hz, 1.6 Hz, 2H), 4.69 (d, *J* = 11.2 Hz, 1H), 5.06 (dd, *J* = 10.8 Hz, 1.6 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 5.32 (dd, *J* = 10.8 Hz, 1.6 Hz, 1H), 7.35−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 139.1, 129.2, 128.9, 128.1, 62.8, 57.1, 55.0, 54.8, 47.6, 13.8; IR (KBr): 3469, 2984, 1745, 1455, 1372, 1267, 1144, 1026, 858, 767, 738, 695, 603, 578, 507 cm^{-1}; HRMS (ESI+) exact mass calculated for $[M+Na]^+$($C_{13}H_{14}Br_4NaO_2$) reqiures *m/z*

540.7620 , found m/z 540.7626.

Procedure for the Preparation of Compound 8. Benzaldehyde (0.20 mmol), Ylide **7** (0.24 mmol) and 4Å molecular sieve (40.0 mg) were added to a flame-dried Schlenk tube. The vessel was placed under vacuum and the atmosphere was exchanged with N_2 three times before dry DCE (0.5 ml) was added. The mixture was stirred under reflux for 24h. Then, oxalyl bromide (0.6 mmol) was added to the stirred reaction mixture. The final reaction mixture was stirred at room temperature for 5h. After the reaction was complete, the reaction mixture was purified by flash column chromatography using petroleum ether/EtOAc to obtain the desired product **8**.

Compound 8.[18] A white solid (16 mg, 22%, d.r. = 8:1); H NMR (400 MHz, $CDCl_3$): δ 5.65 (d, J = 11.2 Hz, 1H), 5.84 (d, J = 11.2 Hz, 1H), 7.36−7.45 (m, 3H), 7.52−7.57 (m, 4H), 7.65−7.68 (m, 1H), 8.11 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 138.2, 134.5, 134.2, 129.3, 129.0, 128.9, 128.9, 128.4, 49.8, 46..8.

Procedure for the Preparation of Compound 10. Wittig salt **9**[19] (0.5 mmol) was added to a Schlenk tube, and then 1.25 mL saturated aqueous $NaHCO_3$ was poured into the tube. The mixture was vigorously stirred for 1h at 30 ^{o}C. Then the crude mixture was extracted with DCM, washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was transferred to a flame-dried Schlenk tube. Then 4Å molecular sieve (40.0 mg), DCE (1.0 mL) and oxalyl bromide (1.5 mmol) were added. The reaction mixture was stirred at 40 ^{o}C for 24h. After the reaction was complete, the reaction mixture was purified by flash column chromatography using petroleum ether/EtOAc (11:1) to

obtain the desired product **10**.

Compound 10.[18] A white solid (14 mg, 9%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.97 (d, *J* = 2.4 Hz, 1H), 5.35 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.23−7.26 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 150.3, 131.6, 128.6, 125.6, 119.9, 117.7, 43.6, 39.2.

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ASSOCIATED CONTENT

Supporting Information

Optimization, copies of spectra and X-ray crystallographic data for **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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