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Solvent-Controlled Oxidative Cyclization for Divergent Synthesis of Highly Functionalized Oxetanes and Cyclopropanes

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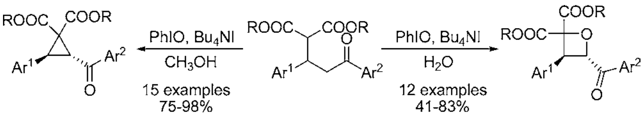
ABSTRACT



An efficient solvent-controlled oxidative cyclization of Michael adducts of malonates with chalcones with the combination of iodosobenzene and tetrabutylammonium iodide is reported. Highly functionalized oxetanes and cyclopropanes were divergently synthesized in moderate to excellent yields with high diastereoselectivity.

The efficient composition of highly strained compounds such as three- or four-membered cycles is of significant synthetic interest.[1−4] Their rigid scaffolds not only appear as important substructures in a large number of medicinally and biologically active natural and unnatural substances but also can undergo a variety of transformations to afford other useful synthetic building blocks.[5] The Michael addition of malonates to α,β-unsaturated ketones is one of the important C−C bond forming reactions that offer access to synthetically useful functionalized organic molecules.[6] In the last decades,

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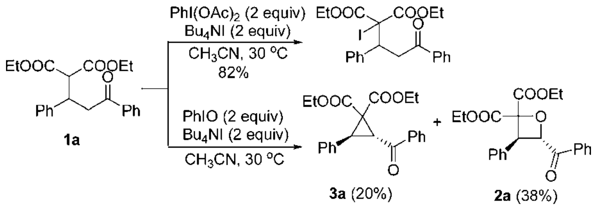
many methods have been developed for the stereoselective reaction.[7] As a result, this transformation is practical for use in organic synthesis. In this communication, we present a solvent-controlled stereoselective oxidative cyclization of Michael adducts of malonates with chalcones for the divergent synthesis of highly functionalized oxetanes and cyclopropanes.

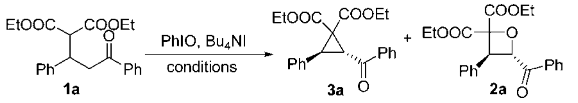
Polyvalent iodine derivatives have been used extensively in organic synthesis as a result of their benign environmental character, ready availability and versatility.[8] Some of our recent efforts[9] have been addressed in the development of synthetic application of iodobenzene diacetate, $PhI(OAc)_2$, to construct aziridines[9b] and nitrocyclopropanes.[9d] With the aim of extending this approach, we investigated the oxidative cyclization of Michael adduct of ethyl malonate with chalcone.

Scheme 1



No cyclopropanation was observed with PhI(OAc)2 as the oxidant under the typical conditions. Interestingly, with iodosobenzene (PhIO) instead of PhI(OAc)2, the desired cyclopropane **3a** was obtained in 20% yield, and an unexpected product, which was identified as the oxetane **2a**, was isolated in 38% yield (Scheme 1).

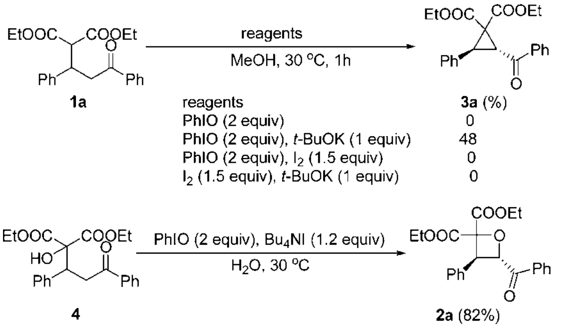
Table 1. Evaluation of Reaction Conditions[a]



entry	conditions	**3a** (%)[b]	**2a** (%)[b]
1	Toluene, 30 °C, 28 h	25	32
2	CH_2Cl_2, 30 °C, 36 h	28	27
3	DMF, 30 °C, 30 h	47	30
4	*t*-BuOH, 30 °C, 10 h	28	26
5	EtOH, 30 °C, 10 h	59	7
6	MeOH, 30 °C, 3 h	90	0
7	H_2O, 30 °C, 128 h	4	60
8	H_2O, 50 °C, 30 h	17	40
9[c]	$C_{12}H_{25}C_6H_4SO_3Na$, H_2O, 30 °C, 128 h	7	0
10	Ultrasonic, H_2O, 30 °C, 128 h	6	0
11[d]	SiO_2, Na_2CO_3 (0.5 equiv), H_2O, 30 °C, 96 h	2	63
12[e]	MeOH, 30 °C, 3 h	92	0
13[f]	SiO_2, Na_2CO_3 (0.5 equiv), H_2O, 30 °C, 96 h	2	68

[a] Reaction conditions: substrate **1a** (0.5 mmol), PhIO (1 mmol), and Bu_4NI (1 mmol), solvent (2 mL), unless noted. [b] Isolated yield based on substrate **1a**. [c] $C_{12}H_{25}C_6H_4SO_3Na$ (100 mg) was added. [d] Na_2CO_3 (0.5 equiv, 0.25 mmol) and silica gel (100 mg) were added. [e] Bu_4NI (1.5 equiv, 0.75 mmol) was used. [f] PhIO (3 equiv, 1.5 mmol) and 1.2 equivalents of Bu_4NI (0.6 mmol), 0.5 equivalents of Na_2CO_3 (0.25 mmol), and silica gel (100 mg) were used.

Scheme 2



Due to Dunitz−Schomaker strain (1,3-carbon−carbon interaction),[10] which is significant in four-membered systems,[11] the efficient synthesis of oxetanes remains a challenge for organic chemists.[4] Motivated by the synthetic potential of the possible method, the reaction was further optimized by examining various reaction conditions, and some of the results are shown in Table 1. Compared with the reactions in polar or nonpolar aprotic solvents, the reactions in alcohols completed in the shorter time. A satisfactory selectivity and isolated yield of cyclopropane **3a** (90% yield) was achieved when methanol was utilized (Table 1, entry 6). When the reaction was carried out in an air-open system with water as the solvent, the reaction gave rise to oxetane **2a** as the major product in 60% yield, albeit in a longer time (Table 1, entry 7). Higher temperature accelerated the reaction but resulted in an inferior result (Table 1, entry 8). Addition of a surfactant or ultrasonic treatment resulted in complicated reactions, and no oxetane **2a** was obtained (Table 1, entries 9 and 10). Moreover, when SiO_2 and Na_2CO_3 (0.5 equiv) were used as the additives, the reaction was accelerated and

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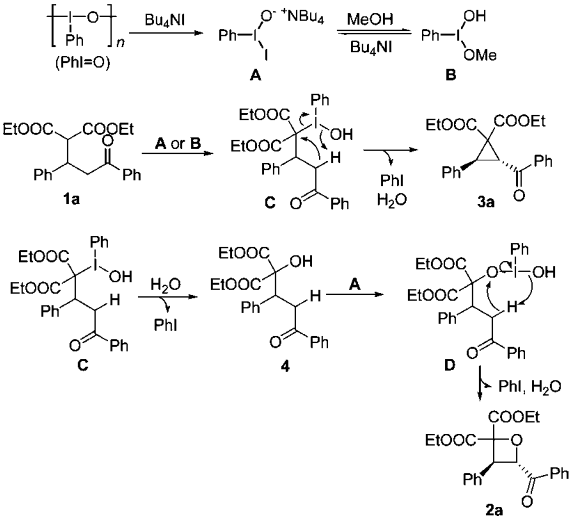
Scheme 3. Plausible Reaction Pathway for the Oxidative Cyclization

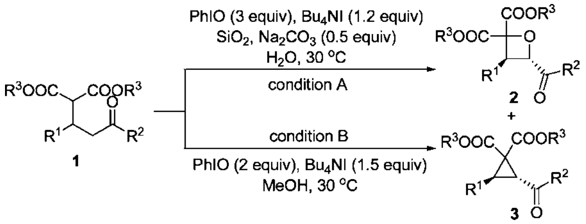


gave rise to a better selectivity and a higher isolated yield of oxetane **2a** (Table 1, entry 11). In the further investigation, we found that the best ratio of substrate, PhIO, and Bu_4NI for the reaction in MeOH was 1:2:1.5, with which the yield of **3a** increased to 92%, while the best ratio for the reaction in H_2O was 1:3:1.2, with which the yield of **2a** increased to 68% (Table 1, entries 12 and 13).

To understand the reaction pathway, several control experiments were conducted (Scheme 2). While no reaction occurred in the absence of Bu_4NI, cyclopropane **3a** was obtained in 48% yield with the combination of PhIO with a base (*t*-BuOK). Although the generation of iodine was observed during the reactions, no cyclopropane or oxetane was formed with I_2 instead of Bu_4NI. The above results indicated that the reaction might not be mediated by I^+. A small amount of 2-hydroxy substituted Michael adduct **4** was detected from the reaction in water. After the purification and identification, compound **4** was treated with PhIO and Bu_4NI in water. The reaction was completed in 24 h and gave rise to oxetane **2a** in 82% yield.

A plausible reaction pathway, which involves the ligand exchange reaction and reductive elimination reaction of organic iodine(III) compounds,[8,12] is outlined in Scheme 3. In the presence of Bu_4NI, polymeric iodosobenzene is depolymerized and generates an oxidizing monomeric species **A**,[13] which can be transformed into an intermediate **B** in MeOH. Michael adduct **1a** reacts with the highly reactive species**A** or**B** via a ligand exchange reaction to form an intermediate **C**, which undergoes an intramolecular reductive elimination to afford cyclopropane **3a**. When the reaction is carried out in water, the intermediate **C** reacts with water to

Table 2. Solvent-Controlled Oxidative Cyclization of Michael Adducts of Malonates with Chalcones



				condition A[a]				condition B[b]			
entry	R^1	R^2	R^3	**2**	yield (%)[c]	**3**	yield (%)[c]	**2**	yield (%)[c]	**3**	yield (%)[c]
1	Ph	Ph	Et	**2a**	68	**3a**	2	**2a**	0	**3a**	92
2	4-MeO−C_6H_4	Ph		**2b**	83	**3b**	3	**2b**	0	**3b**	95
3	4-Me−C_6H_4	Ph		**2c**	70	**3c**	3	**2c**	0	**3c**	96
4	4-Cl−C_6H_4	Ph		**2d**	60	**3d**	12	**2d**	0	**3d**	96
5	2-Cl−C_6H_4	Ph		**2e**	61	**3e**	28	**2e**	0	**3e**	92
6	4-NO_2−C_6H_4	Ph		**2f**	0	**3f**	0	**2f**	0	**3f**	92
7	3-NO_2−C_6H_4	Ph		**2g**	41	**3g**	21	**2g**	0	**3g**	95
8	Ph	4-MeO-C_6H_4		**2h**	73	**3h**	trace	**2h**	0	**3h**	98
9	Ph	4-Me-C_6H_4		**2i**	70	**3i**	trace	**2i**	0	**3i**	98
10	Ph	4-Cl-C_6H_4		**2j**	63	**3j**	21	**2j**	0	**3j**	94
11	Ph	4-NO_2−C_6H_4		**2k**	0	**3k**	68	**2k**	0	**3k**	75
12	4-MeO-C_6H_4	4-Me-C_6H_4		**2L**	66	**3L**	trace	**2L**	0	**3L**	95
13	4-MeO−C_6H_4	4−Cl-C_6H_4		**2m**	71	**3m**	11	**2m**	0	**3m**	96
14	Ph	Ph	Me	**2n**	60	**3n**	trace	**2n**	0	**3n**	94
15	Ph	Ph	^{t}Bu	**2o**	0	**3o**	0	**2o**	0	**3o**	89
16	*t*-Bu	Ph	Et	**2p**	0	**3p**	0	**2p**	0	**3p**	0
17	Ph	CH_3	Et	**2q**	0	**3q**	0	**2q**	0	**3q**	0

[a] Reaction conditions A: substrate **1** (0.5 mmol), PhIO (1.5 mmol), Bu_4NI (0.6 mmol), silica gel (100 mg) and Na_2CO_3 (0.25 mmol), H_2O (2 mL). [b] Reaction conditions B: substrate **1** (0.5 mmol), PhIO (1 mmol), Bu_4NI (0.75 mmol), MeOH (2 mL). [c] Isolated yield based on substrate **1**.

yield 2-hydroxy compound **4**. After the second ligand exchange reaction with **A** to generate an intermediate **D** and its subsequent reductive elimination, oxetane **2a** is formed.

The generality of the present PhIO/Bu_4NI induced divergent oxidative cyclization of Michael adducts of malonates with chalcones was then investigated under the established conditions (Table 2). When the reactions were carried out in water, a moderate electronic substrate effect was observed. Compounds with an electron-donating substituent were better substrates than those with an electron-withdrawing substituent, and their reactions afforded the corresponding oxetanes in better selectivities and yields. This electronic substrate effect accorded with the proposed mechanism. Oxetanes and cyclopropanes are derived from the same intermediate **C**. Due to the higher reactivity of the proton on the carbon alpha to the electron-poor aryl ketone, the intramolecular reductive elimination reaction of the intermediate **C** is preferred to yield cyclopropane. For the electron-rich aryl ketone substrates, the lower reactivity of the corresponding proton leads the intermediate **C** to be readier to undergo the intermolecular reaction with water to yield 2-hydroxy compound and to afford oxtane. No oxetane was obtained from the reactions of *p*-nitro substrates or ditert-butyl malonate derivative. When the reactions were carried out in MeOH, all substrates showed a good reactivity. The corresponding cyclopropanes were generated in good to excellent yields, while no oxetane was detected from the reactions. Aliphatic substrates were unreactive under the same conditions, and no oxetane or cyclopropane was isolated from the reactions (Table 2, entries 16 and 17). All oxetanes and cyclopropanes were formed with a high diastereoselectivity (anti:syn >95:5, determined by ^1H NMR). The anti relative stereochemistry was confirmed by ^1H NMR and the single-crystal diffraction analysis of 2d (Figure 1).

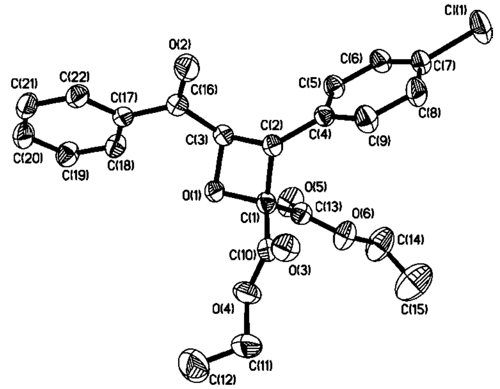


Figure 1. X-ray diffraction structure of **2d**.

In conclusion, we report here an efficient solvent-controlled oxidative cyclization of Michael adducts of malonates with chalcones with the combination of iodosobenzene and tetrabutylammonium iodide. Highly functionalized oxetanes and cyclopropanes are divergently synthesized in moderate to excellent yields with high diastereoselectivity. Current dedication has been made to extend its scope, asymmetric transformations, and possible synthetic applications.

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Supporting Information Available: Experimental details and spectral data for the major products. This material is available free of charge via the Internet at http://pubs.acs.org.

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