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## COMMUNICATION

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# Intermolecular Tandem Addition/Esterification Reaction of Alkenes with Malonates Leading to $\gamma$ -Lactones Mediated by Molecular Iodine under Visible Light Irradiation

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**Abstract.** The iodine-mediated intermolecular C–C bond-forming/esterification reaction of various alkenes including  $\alpha$ -olefins with malonates under irradiation using a compact fluorescent lamp has been developed to synthesize  $\gamma$ -lactones in moderate to excellent yields. The method developed in this research shows broad substrate scope and moderate diastereoselectivity and constructs valuable polyfunctionalized  $\gamma$ -lactones. Furthermore, the developed methodology was comprehensively studied by performing several control experiments, radical trapping, and radical clock experiments. These experiments showed that sequential iodination by an iodine radical is triggered for the following C–C bond-forming reaction. $\gamma$ 

**Keywords:** iodine; lactones; olefins; photochemistry; radical reactions

Polyfunctionalized  $\gamma$ -lactones are commonly found in many naturally occurring compounds and show important biological activities.<sup>[1]</sup> The structure of  $\gamma$ lactone is also present in a diverse range of agrochemicals and pharmaceuticals.<sup>[2]</sup> Therefore, various methods to synthesize lactones have been developed *via* cyclization reaction of linear starting materials.<sup>[3]</sup> Moreover, the enantioselective ketone hydroacylation reaction from keto alcohol leading to the formation of  $\gamma$ -lactones has been reported.<sup>[4]</sup> Despite the significant progress made in the synthesis of lactones *via* cyclization reaction, multi-step syntheses to obtain linear starting materials are often required.

Therefore, the diversity-oriented and straightforward methodologies leading to γ-lactones are highly desirable. For direct construction of γ-lactones from readily available substrates, oxidative transformation provides a privileged methodology.<sup>[5]</sup> Jiang and coworkers reported Cu-catalyzed or Mn-mediated intermolecular oxidative cycloaddition of alkene with anhydrides (Scheme 1a).<sup>[6]</sup> Although this transformation shows a broad substrate scope for direct synthesis of lactones, the process requires a heavy

metal reagent, higher reaction temperature, and the unpredictable diastereoselectivity. The pioneering research by Wu and Liu on the lactonization reaction of styrenes with  $\alpha$ -halo esters utilized Ir(III) photoredox catalysis (Scheme 1b).<sup>[7]</sup> However, their method required halogenation of  $\alpha$ -carbonyls to generate a *C*-centered radical and an expensive and potentially toxic transition metal-based photoredox catalyst.<sup>[8]</sup> Therefore, the methods that are straightforward, convenient, and mild leading to the formation of  $\gamma$ -lactones are highly desirable.





**Scheme 1.** Direct synthesis of lactones via olefin difunctionalization reaction.

We have focused on visible light-mediated transformations and have reported several reactions based on photooxidative/photoexcitation strategy.<sup>[9]</sup> In our previous study on the photooxidative dehydrogenative C–C bond-forming reaction of heteroarenes with malonate, we found that the exposure of olefin-bearing pendant malonate to the

optimized condition afforded bicyclic butyrolactone (Scheme 1c).<sup>[10]</sup> This result indicates that the intramolecular C–C bond formation occurred between malonate with olefin in *5-exo-trig* manner. Subsequently, the following C–O bond formation produced corresponding lactones. We envisioned that a direct lactonization reaction could be realized if the intermolecular C–C bond formation between malonate with olefins occurs under similar reaction condition (Scheme 1d).

Herein, we report that the combination of visible light and molecular iodine is an efficient mediator of the intermolecular C–C/C–O bond formation between olefins with malonates, leading to the formation of lactones. This method also shows moderate *cis* diastereoselectivity.

We initiated our research by focusing on the direct lactonization reaction of styrene (1a) with methyl dimethylmalonate (2a) irradiated with visible light using a compact fluorescent lamp (CFL) (Table 1).

**Table 1.** Optimization study of lactone synthesis meditated by iodine/visible light.

Ph 🔷 🕯	$Ae + CO_2Me + CO_2M$	0 equiv) $DH_{2}(1.0 equiv)$	
1a	2a Ar, rt	, 20 h <b>3a</b>	-cis 3a-trans
entry	solvent	yield (%) <sup>[a]</sup>	dr (cis:trans) <sup>[b]</sup>
1	MeOH	17	33:67
2	EtOH	67 <sup>[c]</sup>	48:52
3	IPA	85 <sup>[c]</sup>	58:42
4	<sup>t</sup> AmylOH	74	64:34
5	<sup>t</sup> BuOH	83	79:21
6 <sup>[d]</sup>	<sup>t</sup> BuOH	23	70:30
7 <sup>[e]</sup>	<sup>t</sup> BuOH	no reaction	-
8 <sup>[f]</sup>	<sup>t</sup> BuOH	no reaction	-

<sup>[a]</sup> Isolated yield.

<sup>[b]</sup> Diasteromeric ratios were determined by <sup>1</sup>H NMR analysis of crude reaction mixture.

<sup>[c]</sup> Transesterification product was also included.

<sup>[d]</sup> 0.5 equiv of I<sub>2</sub> was used.

<sup>[e]</sup> Without Ca(OH)<sub>2</sub>.

<sup>[f]</sup> Without iodine.

The mixture of **1a**, **2a**, and molecular iodine with  $Ca(OH)_2$  in solvent was stirred for 20 h (refer to S1 for full details of optimization). Extensive experiments revealed that the yield of corresponding lactone (**3a**) was significantly affected by the use of the solvent. We found that the use of a protic solvent, MeOH, was effective for the reaction (Table 1, entry 1). To improve on this result, a series of protic solvents, including EtOH, IPA, 'Amyl-OH, and 'Bu-OH, were evaluated in this reaction, among which 'Bu-OH was the most effective in generating the desired product with 83% yield and 79:21 diastereoselectivity (entries 2–5). In addition, loading 0.5 equiv of iodine displayed a significant decrease in the reaction efficiency, furnishing product **3a** in 23% yield (entry 6). Finally,

control experiments performed without iodine or  $Ca(OH)_2$  resulted in no reaction (entries 7 and 8, respectively), thus indicating that the combination of iodine and base is crucial for this lactonization reaction.

Employing the optimized reaction conditions, we evaluated the generality of the process. Table 2 summarized results of the reaction using various olefins 1. Whether alkyl or halogen substituents on styrenes, the reaction proceeded to give the corresponding lactones 3 in moderate to good yield with moderate dr values, respectively (Table 2, entries 1-8). Substrate 1i bearing ester group afforded the desired product in 64% yield with similar diastereoselectivity (entry 9). Only in the case of 1j, polymerization of **1** predominantly occurred, perhaps due to the strongly electron-donating MeO group on the styrene (entry 10). To our delight, the reaction also tolerated substrates 1 with different aryl groups, leading to desired lactones 3k-m in moderate yields with moderate dr (entries 11-13). Finally, the reaction was also applicable to  $\alpha$ -olefin such as 1-dodecene (1n) to give lactone 3n in good yield (entry 14).

**Table 2.** Substrates scope using various olefins 1 with 2a<sup>[a]</sup>

R 🔦 .	+ Me	CO <sub>2</sub> Me	I <sub>2</sub> (1.0 equiv) Ca(OH) <sub>2</sub> (1.0 <sup>t</sup> BuOH, Ar	equiv)		) ∳_CO₂Me Me	
1		2a	20 h, CFL		3		
entry	1	R		3	yield	dr <sup>[c]</sup>	
					$(\%)^{[b]}$		
1	1a	Ph		3a	83	79:21	
2	1b	$4-^{t}Bu$	$C_6H_4$	3b	65	76:24	
3	1c	4-Me	$C_6H_4$	3c	46	72:28	
4	1d	3-Me	$C_6H_4$	3d	64	69:31	
5	1e	2-Me	$C_6H_4$	3e	76	74:26	
6	1f	$4-FC_6H_4$		3f	40	71:29	
7	1g	$4-ClC_6H_4$		3g	62	75:25	
8	1h	4-BrC <sub>6</sub> H <sub>4</sub>		3h	57	70:30	
9	1i	4-Me	$O_2CC_6H_4$	3i	64	68:32	
10	1j	4-Me	$OC_6H_4$	3j	trace		
11	1k	4-PhC	$L_6H_4$	3k	57	82:18	
12	11	2-Nap	h	31	47	73:27	
13	1m	2-pyri	dyl	3m	51	38:62	
14	1n	$C_{10}H_2$	1	3n	82	67:33	

<sup>[a]</sup> Reaction condition: **1** (2 equiv), **2a** (0.3 mmol), I<sub>2</sub> (0.3 mmol), and Ca(OH)<sub>2</sub> (0.3 mmol) in 'BuOH (3 mL) and stirred at ambient temperature irradiated with a compact fluorescent lamp (CFL) for 20 h.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> Diasteromeric ratios were determined by <sup>1</sup>H NMR analysis of crude reaction mixture.

Using styrene **1a** as the substrate, we subsequently investigated the scope of malonate **2** to elucidate the effect of the substituents on malonates (Table 3).

This intramolecular lactonization reaction smoothly proceeded with the sterically hindered substrate 30 but in lower diastereoselectivity (Table 3, entry 1 vs. entry 2). However, substrates bearing a benzyl group 3p or phenethyl group 3q afforded the corresponding

product in lower yield with slightly higher diastereoselectivity compared with 3a (entries 3 and 4). Unfortunately, this system was unable to facilitate the lactonization reaction using triethyl methanetricarboxylate 3r at this stage (entry 5). The ester-bearing sterically hindered <sup>t</sup>Bu group produced lactones with low yield and excellent diastereoselectivity (entry 6). Gratifyingly, further substrate scope studies revealed that while the reaction of methyl 2-methylacetoacetate readily proceeded and gave the O-cyclization product 3t in 66% yield (entry 7), the corresponding 2-methylacetoacetic acid was not effective for the desired C-C bond forming reaction (entry 8).

 Table 3. Scope of substrates using styrenes 1a with various malonates 2.

Ph	$\land$ , $\mathbb{R}^{1}$	R <sup>2</sup>	I <sub>2</sub> (1. Ca(C	0 equiv) 0H) <sub>2</sub> (1.0	equiv)		$R^2$
	ċc	$P_2R^3$	<sup>t</sup> BuO	H, Ar		Ph	R <sup>1</sup>
1a 2			20 h, CFL		3		
	D	<b>D</b> <sup>2</sup>		<b>D</b> <sup>3</sup>		2.1.1	I [b]
entry	K'	K²		K <sup>3</sup>	3	yield	$ar^{o}$
						(%) <sup>[a]</sup>	
1	Me	$CO_2$	Me	Me	3a	83	79:21
2	Ph	$CO_2$	Me	Me	30	60	62:38
3	Bn	$CO_2$	Me	Me	3p	30	86:14
4	$Ph(CH_2)_2$	$CO_2$	Me	Me	3q	44	85:15
5	CO <sub>2</sub> Et	$CO_2I$	Et	Me	3r	trace	-
6	Me	$\mathrm{CO}_2^t$	Bu	Me	3s	35	95:5
7	Me	COM	1e	Me	3t	66	50:50
8	Me	COM	ſe	Η	3t	8	50:50
	1 1 1 1						

<sup>[a]</sup> Isolated yield.

<sup>[b]</sup> Diasteromeric ratios were determined by <sup>1</sup>H NMR analysis of crude reaction mixture.

Furthermore, we focused on elucidating the reaction mechanism (Scheme 2, refer to S2-4 for full details of these study). First, the role of iodine was investigated (Eq. 1). The reaction using cationic iodine source, such as NIS or  $(lutidine)_2 I^+ BF_4^-$ , instead of molecular iodine under optimized reaction condition significantly decreased the yield of **3a**.<sup>[11]</sup> However, two equivalents of NIS produced similar yield of the product. Trace amount of the product was observed when the reaction condition was changed to the heating and dark conditions. These observations revealed that olefin was not activated by cationic iodine to form iodonium intermediate and that visible light from the CFL could increase the reaction efficiency. Then, we investigated whether iodinated malonate 2a-I, which we previously reported as the C-centered radical source, is generated (Eq. 2).<sup>[9i, 10]</sup> The reaction of **2a-I** with styrene under optimized reaction condition resulted in no reaction. To determine the key intermediate, the reaction under an oxygen atmosphere was conducted (Eq. 3). Phenacyl iodide 4a, which was synthesized by the addition of iodine radical to styrene and by the addition of triplet oxygen to benzyl radical generated followed by dehydration, was obtained in 34% yield.<sup>[12]</sup> Therefore, we hypothesized that the visible light promotes the generation of iodine radicals and that the generated iodine adduct is intermediate for the reaction. To gain more insight regarding the mechanism, 1-cyclopropyl-1-phenylethylene was subjected to our standard condition; the ring-opening products **5a** and **5b** were obtained (Eq. 4). This result clearly confirms the generation of an iodine radical intermediate.

On the basis of the results of these investigations, a tentative mechanism is proposed in Scheme 3. Molecular iodine and the iodine radical are in equilibrium under visible right irradiation, and the generated radical is sequentially added to styrene to yield **II**. *vic*-Diiodoalkanes **II**, generated *in situ*, are generally unstable and tend to revert back to iodine and the olefin.<sup>[13]</sup> In the presence of Ca(OH)<sub>2</sub>, compound **II** reacts with malonate **2a**, affording the corresponding product **III**. Finally, cyclization produces the desired lactone **3**.









Scheme 3. Proposed mechanism for lactonization.

In brief, we developed a photoinitiated method for the constructing polysubstituted  $\gamma$ -lactones *via* an iodine-mediated C–C/C–O bond-forming sequence. The highlight of this operationally straightforward reaction is the avoidance of transition or heavy metal reagent, use of abundant molecular iodine, and generation of  $\gamma$ -lactone in high yields under mild conditions. Moreover, the diastereoselectivity of the desired lactones can be controlled by using an alkaline metal or alkaline earth metal. Further studies on the scope, more detailed mechanism, and synthetic applications of this novel iodine/visible light chemistry are under investigation in our laboratory.

#### **Experimental Section**

**General procedure:** A Pyrex<sup>®</sup> test tube (16.5 cm × 1.5 cm) containing a mixture of dimethyl 2-methylmalonate **2** (0.3 mmol),  $I_2$  (76.2 mg, 1.0 epuiv., 0.3 mmol), calcium hydroxide (22.2 mg, 1.0 equiv, 0.3 mmol) and styrene **1** (2.0 equiv, 0.6 mmol) in *tert*-butyl alcohol (3.0 mL) was degassed *via* FPT cycling for three times and backfilled with Ar. The resulting solution was stirred at ambient temperature for 20 h. The reaction was quenched with sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aq. and extracted with Et<sub>2</sub>O (10 mL x 3). The combined organic layers were washed with brine, dried over Mg<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting mixture was purified by flash column chromatography on silica gel (*n*-hexane : EtOAc) to give **3**.

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#### References

- [1] a) H. M. R. Hoffmann, J. Rabe, Angew. Chem. 1985, 97, 96-112; Angew. Chem. Int. Ed. 1985, 24, 94-110. b) A. K. Picman, Biochem. Syst. Ecol. 1986, 14, 255-281.
- [2] a) E. M. Mangnus, B. J. Zwanenburg, *Agric. Food Chem.* 1992, 40, 1066-1070. b) G. H. L. Nefkens, J. W. J. F. Thuring, M. F. M. Beenakkers, B. J. Zwanenburg, *Agric. Food Chem.* 1997, 45, 2273-2283. c) B. Fang, X. Xie, C. Zhao, P. Jing, H. Li, Z. Wang, J. Gu, X. She, J. Org. *Chem.* 2013, 78, 6338-6343.
- [3] a) S. K. Taylor, N. H. Chmiel, L. J. Simons, J. R. Vyvyan, J. Org. Chem. 1996, 61, 9084-9085. b) T. Dohi, N. Takenaga, A. Goto, A. Maruyama, Y. Kita, Org. Lett. 2007, 9, 3129-3132. c) L. J. Goobn, D. M. Ohlmann, M. Dierker, Green Chem. 2010, 12, 197-200. d) N. Tada, T. Ishigami, L. Cui, K. Ban, T. Miura, A. Itoh, Tetrahedron Lett. 2013, 54, 256-258. e) V. Valerio, D. Petkova, C. Madelaine, N. Maulide, Chem. Eur. J. 2013, 19, 2606-2610. f) H. K. Grover, M. R. Emmett, M. A. Kerr, Org. Lett. 2013, 15, 4838-4841. g) J. Li, S. Yang, H. Jiang, W. Wu, J. Zhao, J. Org. Chem. 2013, 78, 12477-12486. h) A. Díaz-Rodríguez, W. Borzcka, I. Lavandera, V. Gotor, ACS Catal. 2014, 4, 386-393. i) N. Sakai, S. Horikawa, Y. Ogiwara, RSC Advances 2016, 6, 81763-81766.
- [4] S. K. Murphy, V. M. Diong, J. Am. Chem. Soc. 2013, 135, 5553-5556.

- [5] a) J. R. Peterson, H. D. Do, I. B. Surjasasmita, Synth. Commun. 1988, 18, 1985-1993. b) A. Citterio, R. Sebastiano, M. Nicolini, R. Santi, Synlett 1990, 42-43. c) J. R. Peterson, H. D. Do, R. D. Rogers, Synthesis 1991, 275-277. d) E. Baciocchi, R. Ruzziconi, J. Org. Chem. 1991, 56, 4772-4778. e) M. Allegretti, A. D'Annibale, C. Trogolo, Tetrahedron 1993, 49, 10705-10714. f) V. Nair, J. Mathew, J. Org. Soc. Perkin. Trans. 1 1995, 1881-1882. g) M. Horikawa, H. Shirahama, Synlett 1996, 95-96. h) V. Nair, J. Mathew, L. G. Nair, Synth. Commun. 1997, 27, 3053-3064. i) L. Huang, H. Jiang, C. Qi, X. Liu, J. Am. Chem. Soc. 2010, 132, 17652-17654. (j) D. Hulya, A. Mustafa, Z. Mustafa, K. Mustafa, Lett. Org. Chem. 2011, 8, 488. (k) R. Matsumoto, H. Nishino, Synth. Commun. 2015, 45, 1807. 1) X.-J. Wei, D.-T. Yang, L. Wang, T. Song, L.-Z. Wu, Q. Liu, Org. Lett. 2013, 15, 6054-6057. (m) G. Fumagalli, S. Boyd, M. F. Greaney, Tetrahedron Lett. 2015, 56, 2571-2573.
- [6] a) L. Huang, H. Jiang, C. Qi, X. Liu, J. Am. Chem. Soc. 2010, 132, 17652. (b) L. Wu, Z. Zhang, J. Liao, J. Li, W. Wua, H. Jiang, Chem. Commun. 2016, 52, 2628.
- [7] X.-J. Wei, D.-T. Yang, L. Wang, T. Song, L.-Z. Wu, Q. Liu, Org. Lett. 2013, 15, 6054-6057.
- [8] H. Kruszyna, R. Kruszyna, J. Hurst, R. P. J. Smith, *Toxicol, Environ. Health.* 1980, 6, 757-773.
- [9] a) N. Kanai, H. Nakayama, N. Tada, A. Itoh, Org. Lett. 2010, 12, 1948-1951. b) N. Tada, M. Shomura, L. Cui, T. Nobuta, T. Miura, A. Itoh, Synlett 2011, 19, 2896-2900. c) N. Tada, T. Ishigami, L. Cui, K. Ban, T. Miura, A. Itoh, Tetrahedron Lett. 2013, 54, 256-258. d) Y. Nagasawa, Y. Matsusaki, T. Hotta, T. Nobuta, N. Tada, T. Miura, A. Itoh, Tetrahedron Lett. 2014, 55, 6543-6546. e) Y. Tachikawa, Y. Nagasawa, S. Furuhashi, L. Cui, E. Yamaguchi, N. Tada, T. Miura, A. Itoh, RSC. Adv. 2015, 5, 9591-9593. f) Y. Sugiura, Y. Tachikawa, Y. Nagasawa, N. Tada, A. Itoh, RSC Adv. 2015, 5, 70883-70886. g) K. Usami, Y. Nagasawa, E. Yamaguchi, N. Tada, A. Itoh, Org. Lett. 2016, 18, 8-11. h) T. Yamaguchi, K. Sakairi, E. Yamaguchi, N. Tada, A. Itoh, RSC. Adv. 2016, 6, 56892-56895. i) Y. Sudo, E. Yamaguchi, A. Itoh, Org. Lett. 2017, 19, 1610-1613.
- [10] E. Yamaguchi, Y. Sudo, N. Tada, A. Itoh, Adv. Synth. Catal. 2016, 358, 3191-3195.
- [11] When (lutidine)<sub>2</sub>I<sup>+</sup>BF<sub>4</sub><sup>-</sup> was used for the reaction, only the corresponding iodohydrin was obtained (full details are shown in S2). The result showed that the reaction did not proceed *via* an iodonium intermediate.
- [12] T. Nobuta, S. Hirashima, N. Tada, T. Miura, A. Itoh, *Synlett* **2010**, 2335-2339.
- [13] a) M. Zanger, J. L. Rabinowitz, J. Org. Chem. 1975, 40, 248-250. b) J. Barluenga, M. A. Rodriguez, P. J. Campos, G. Asensio, J. Chem. Soc. Chem. Commun. 1987, 1491-1492.

#### COMMUNICATION

Intermolecular tandem addition/esterification reaction of styrenes with malonates leading to  $\gamma$ -lactones mediated by molecular iodine

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up to 83% yield moderate to good diastereoselectivity 19 examples