CHEMISTRY
AN ASIAN JOURNAL
www.chemasianj.org

Accepted Article

Title: TBAI/TBHP-Promoted Generation of Malonyl Radicals: Oxidative Coupling with Styrenes Leads to γ-Keto Diesters

Authors: Soumitra Maity, Soumyadeep Roy Chowdhury, and Injamam Ul Hoque

To be cited as: *Chem. Asian J.* 10.1002/asia.201800992

Link to VoR: http://dx.doi.org/10.1002/asia.201800992

A Journal of
ACES
Asian Chemical Editorial Society

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

WILEY-VCH

COMMUNICATION

TBAI/TBHP-Promoted Generation of Malonyl Radicals: Oxidative Coupling with Styrenes Leads to γ-Keto Diesters

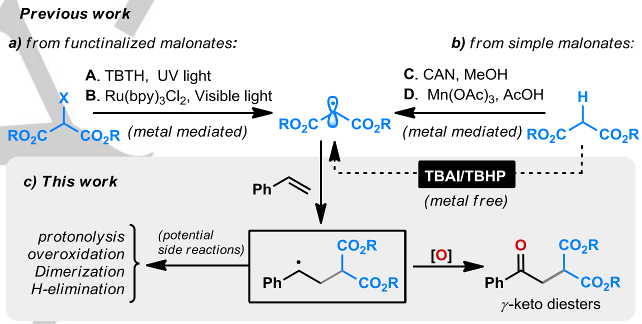
Soumyadeep Roy Chowdhury, [a] Injamam Ul Hoque, [a] and Soumitra Maity*[a]

Dedication ((optional))

Abstract: A metal-free protocol for oxidative coupling of malonic esters with styrenes to form γ-keto diesters has been developed. Key to the success of this process is the generation of malonyl radicals from unfunctionalized malonic esters under organo-catalysis conditions with TBAI and TBHP. This process tolerates both terminal and internal olefins with diverse malonic esters. It provides a new green metal-free alternative to traditional metal mediated process for generation of malonyl radicals and there by γ-keto diesters.

Malonyl radicals are valuable reactive intermediates that can be used as a starter in radical cascade reactions[1] to synthesize complex molecules relevant to natural products, drug discovery and material science.[2] In addition, malonyl radicals are widely used in γ-lactone synthesis.[3] However their generation in mild reaction conditions has been challenging. Traditionally, malonyl radicals are generated from prefuctionalized halo- or seleno-malonates under relatively harsh reaction conditions like, UV light irradiation and/or by using very toxic alkyltin reagents (Scheme 1a).[2a, 4] Recently, visible light mediated photoredox catalysis has enabled malonyl radical generation under mild conditions, however these methods require expensive heavy metal photocatalysts.[1e, 5] Direct generation of malonyl radicals from malonic esters are rare[6] and often characterized by using stoichiometric amount of metal salts like, Ceric ammonium nitrate (CAN),[7] Manganese acetate[8] and iron perchlorate[3a, 3c] in acidic medium (Scheme 1b). Moreover, these radical initiators often lack the chemoselectivity and functional group compatibility. To explore the high synthetic value of malonyl radicals, a new synthetic method is highly desirable that extends beyond the existing route to access them.

γ-keto diesters themselves are important molecules in the chemical, biochemical, and material sciences.[9] Conventional routes to this class of molecules include the nucleophilic substitution of malonate to α-halogenated ketones.[9] Alternatively, oxidative radical difunctionalization of cheap and readily available alkenes[10] with simple malonates might provide a better route to access them. While difunctionalization of styrenes with α-cyanoesters[10c], β-ketoesters[10d, 10g] and 1,3-dicarbonyl compounds[10h-j] have been quite known, reports showing similar coupling with malonic esters are scarce. Only one example to date is reported in the literature by Nair,[11] where CAN was used to activate the malonate-C-H bond and to install the keto functionality into styrene. Additionally, the reaction is not chemoselective, often furnish overoxidation products[12] and limited to terminal styrenes only. Therefore development of efficient methods with broad substrate scope for this transformation is needed.



Scheme 1. a, b) Generation of malonyl radicals. c) Metal free generation of malonyl radicals and coupling with styrenes.

In the past decade, various synthetic methods have been developed that utilize metal-free organo-iodides as a replacement of metal catalysts to drive organic reactions in enviro-economic conditions.[13] Along these lines, tetrabutylammonium iodide (TBAI) in combination with tert-butyl hydroperoxide (TBHP) have been used as a unique oxidation system to generate C-centre radicals, where *in situ* generated ^{t}BuOO• radical served as the key intermediate.[14] Herein, we report for the first time, TBAI/TBHP mediated coupling of styrenes with unfunctionalized malonic esters to give γ-keto diesters through oxidative generation of malonyl radical in the absence of metal with broad substrate scope (Scheme 1c). From the synthetic stand point, current method is simple and unique to generate malonyl radicals and their subsequent addition to olefins leading to a C-C single bond and a C=O double bond in excellent regioselectivity.

We initially investigated the coupling reaction with 4-*tert*-butyl styrene (**1a**) and dimethyl malonate (DMM) (**2a**) as the model substrates (Table 1).[15] In the presence of TBAI, TBHP and triethyl amine, the desired product γ-keto diester **3a** was isolated in 15% yield within 3h at 120 °C (entry 1). To improve the yield, several other bases, including organic and inorganic, were examined (entries 2–5).

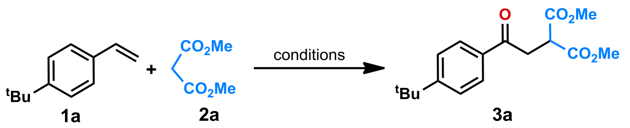
---

[a] Soumyadeep Roy Chowdhury, Injamam Ul Hoque, Dr. Soumitra Maity
Department of Applied Chemistry
Indian Institute of Technology (ISM) Dhanbad
Dhanbad 826004, JH, India
E-mail:smaity@iitism.ac.in

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

10.1002/asia.201800992

Table 1. Optimization of the reaction conditions. [a]



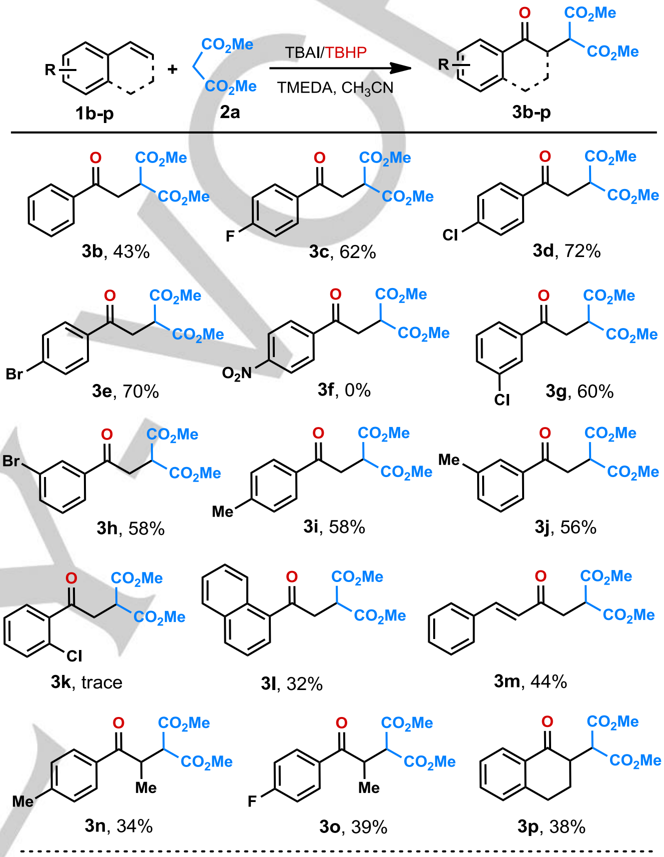
Entry	Catalyst	Oxidant[e]	base	Solvent	Yield (%) [b]
1	TBAI	TBHP	Et_3N	MeCN	15
2	TBAI	TBHP	DBU	MeCN	20
3	TBAI	TBHP	Py	MeCN	7
4	TBAI	TBHP	K_2CO_3	MeCN	0
5	TBAI	TBHP	TMEDA	MeCN	65
6	TBAI	DTBP	TMEDA	MeCN	0
7	TBAI	BPO	TMEDA	MeCN	0
8	TBAI	$K_2S_2O_8$	TMEDA	MeCN	0
9	TBAB	TBHP	TMEDA	MeCN	trace
10	I_2	TBHP	TMEDA	MeCN	0
11	TBAI	TBHP	TMEDA	DCE	30
12	TBAI	TBHP	TMEDA	THF	20
13	TBAI	TBHP	TMEDA	DMF	0
14	TBAI	TBHP	TMEDA	DMSO	0
15[c]	**TBAI**	**TBHP**	**TMEDA**	**MeCN**	**68**
16	-	TBHP	TMEDA	MeCN	0
17	TBAI	-	TMEDA	MeCN	0
18	TBAI	TBHP	-	MeCN	0
19[d]	TBAI	TBHP	TMEDA	MeCN	5

[a] Unless otherwise noted, all reactions were carried out with: **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst (20 mol%), oxidant (3.0 equiv), base (3.0 equiv) and solvent (2 mL) in a pressure tube at 120 °C for 3 h under N_2. [b] Isolated yield. [c] 4Å Molecular sieves, dust (2 wt %). [d] in air. [e] TBHP 5.5 M in decane.

Gratifyingly, switching the organic base to TMEDA enhanced the reaction efficiency to furnish **3a** in 65% yield, but other bases, particularly inorganic bases were completely ineffective.[16] Subsequently, we examined the oxidants, finding that TBHP only exhibited the requisite activity among other peroxides (entry 5 *vs* entries 6–8). Further optimization by changing promoter and solvent did not improve the yield of **3a** (entries 9–14). Interestingly, when 4Å molecular sieves were employed as the additive, a decent 68% yield was observed (entry 15). Control studies showed that the catalyst, oxidant, and base were all essential for this transformation (entries 16–18). The yield of **3a** diminished sharply when the reaction was performed in air, implying the detrimental effect of aerial oxygen in this reaction (entry 19). Additional optimization by changing reaction temperature and reactants ratio didn't add any improvement in yield (entries 18-21 and 26, Table S1).[15]

With suitable conditions in hand, the substrate scope of the metal-free coupling reaction was investigated. As shown in Scheme 2, the transformation generally proceeded to produce the desired γ-keto diesters in moderate to good yields. Styrenes having electron-withdrawing substituents such as halogens (-F, -Cl, and -Br) at the *para*-position afforded the desired products (**3c**–**e**) in good yields. However, when strong electron-withdrawing 4-nitrostyrene (**3f**) was used as substrate, no desired product was formed.

Scheme 2. Scope of styrenes [a]

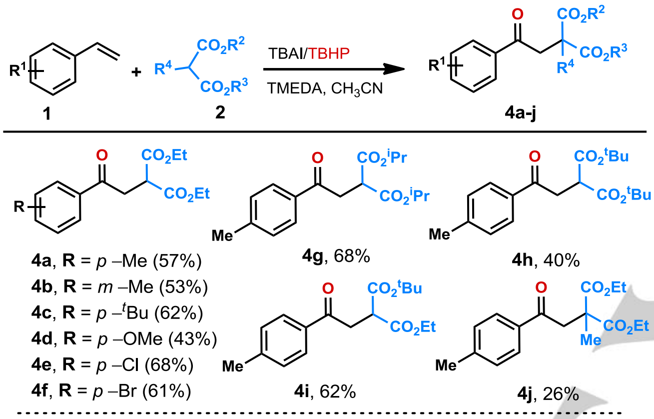


[a] Conditions: **1** (0.4 mmol), **2a** (0.2 mmol), TBAI (20 mol%), TBHP (3.0 equiv), TMEDA (3.0 equiv), 4Å Molecular sieves (2 wt %) and degassed CH_3CN (2 mL) in a pressure tube at 120 °C for 3 h under N_2.

Other halo-styrenes with substitution at the *meta*-position also afforded the desired products (**3g**–**h**). Styrenes having electron-donating substituents such as -CH_3 (**3i** and **3j**) were also tolerated under the reaction conditions. Unfortunately, when *ortho*-substituted styrene (**3k**) or more congested 2-vinylmesitylene was used as a substrate in the reaction, the yield was drastically reduced to trace or even nil. We speculated that steric effect was one of the crucial factor to this reaction. Interestingly, bulky 1-vinylnaphthalene poses no difficulty and gave the desired product **3l**, albeit lower yield. Moreover, the conjugated diene, 1-phenyl-1,3-butadiene participated in the coupling, which occurred regioselectively at the terminal double bond to provide γ-keto diesters **3m**. To test the positional compatibility of the styrene, we applied the protocol to internal olefins which are a part of acyclic or cyclic systems. Reaction with internal vinylarenes afforded γ-keto diesters **3n**–**p** in moderate yield, demonstrating the compatibility of this oxidative coupling protocol with terminal as well as internal styrenes. But the poor productivity of internal olefins (**3n**–**p**) compared to the terminal one (**3n** vs **3i**, **3o** vs **3c**) could be due to steric reason. Unfortunately, no reaction occurred when aliphatic alkenes were employed as the substrate in the above transformation.

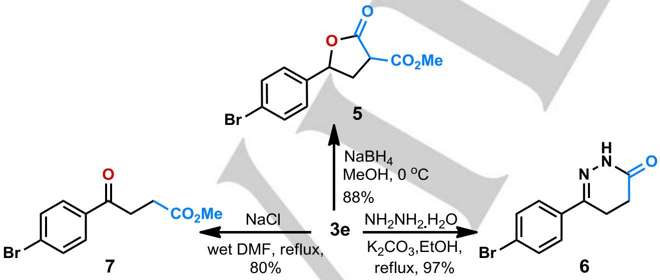
Next, we focused on the scope of malonic esters. As exemplified in Scheme 3, a range of structurally diverse malonates were readily implementable with substituted styrenes to provide their corresponding products (**4a**–**j**) in moderate to good yields. Importantly, γ-keto diester **4i**, a product of mixed malonate, is synthetically highly useful for chemoselective functionalization of the ester groups.[17] In addition, sterically crowded tertiary malonate (**4j**) was also successful in this protocol, allowing direct access to desired product having a β- quaternary carbonyl substitution. Unfortunately, no product was formed when other carbonyl compounds, such as ethyl acetoacetate, ethyl cyanoacetate and acetylacetone were employed as substrate.

Scheme 3. Scope of malonic esters. [a]



[a] Conditions: **1** (0.4 mmol), **2** (0.2 mmol), TBAI (20 mol%), TBHP (3.0 equiv), TMEDA (3.0 equiv), 4Å Molecular sieves (2 wt %) and degassed CH_3CN (2 mL) in a pressure tube at 120 °C for 3 h under N_2.

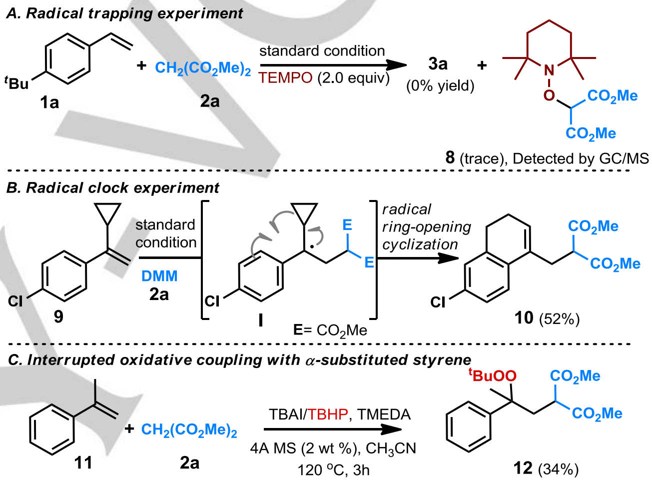
To further showcase the utility of the present oxidative-coupling process, some valuable synthetic transformations were executed using **3e** (Scheme 4). Reduction of **3e** with $NaBH_4$ provided γ-lactone **5** in excellent yield.[9e] When **3e** was treated with hydrazine, imino-amidation followed by decarboxylative cyclization afforded dihydropyridazinone **6**. These scaffolds are of great importance in medicinal chemistry but are challenging to access synthetically.[18] Dealkoxycarbonylation[19] of malonate ester **3e** converted to γ-keto ester **7**, which further expand the potential use of malonic esters as alkylacetate coupling partners.[20]



Scheme 4. Diversification of **3e**.

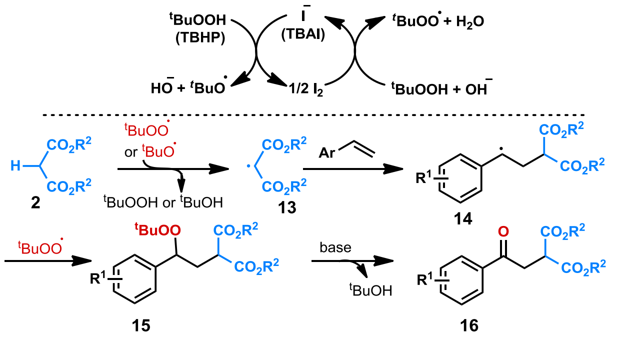
In order to gain preliminary insights into the reaction mechanism, few mechanistic studies were designed and performed (Scheme 5). When the reaction of 4-*tert*-butyl styrene **1a** with dimethyl malonate **2a** was carried out under standard condition (Table 1, entry 15) in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 2 equiv), the formation of **3a** was completely inhibited. Subsequently, the TEMPO-adduct **8** was detected by the GC/MS analysis of the crude product (Scheme 5A), implying the involvement of a carbon radical intermediate. To further validate this radical intermediate, the radical clock experiment was performed (Scheme 5B). It was found that the reaction of α-cyclopropyl-4-chlorostyrene **9** with DMM under standard reaction conditions provided dehydronaphthalene **10**, resulted from the ring-opening cyclization of cyclopropylmethyl radical **I** at the phenyl ring.[21] This reveals strong support for the participation of the manonyl radical in this transformation. As the reaction inhibited under aerobic conditions (Table 1, entry 19), suggesting the source of keto-oxygen in the γ-keto diester is from the reagents. To confirm this, a controlled reaction of α-methylstyrene **11** with **2a** was carried out under standard conditions with an idea to interrupt the oxidative conversion to end keto product (Scheme 5C). As expected the γ-peroxydiester **12** was isolated in 34% yield, confirming the dual roles of TBHP as the terminal oxidant and source of the keto-oxygen incorporated into the product.

The present investigations coupled with the previous reports[10a, e-f] collectively suggest a plausible reaction mechanism as shown in Scheme 6. Initially, the catalytic cycle of TBAI/TBHP promotes the decomposition of TBHP to *tert*-butoxyl and/or *tert*-butylperoxyl radicals which abstract the α-H atom of malonic ester **2** to generate the malonyl radical **13**. Addition of the malonyl radical to the double bond of styrene afforded a transient radical **14**, which selectively couples with ^{t}BuOO• (Ingold-Fischer “Persistent Radical Effect”[22]), to generate peroxide intermediate **15**. Meanwhile, the oxidation of radical **14** followed by trapping of a benzylic carbocation by TBHP under basic conditions to dialkylperoxide **15** could not



Scheme 5. Mechanistic studies.

be excluded. Finally, **15** in presence of base is converted (Kornblum-DeLaMare rearrangement[23]) into the γ-keto diester **16**. The beneficiary role of molecular sieves may scavenge the water, which have been formed in TBAI/TBHP catalytic cycle.



Scheme 6. Plausible reaction mechanism.

In conclusion, a simple and efficient approach to the synthesis of γ-keto diester via oxidative coupling of styrenes with malonic esters has been developed. A catalytic amount of cost-effective TBAI in combination with TBHP efficiently coupled a variety of malonic esters with styrenes in moderate to good yields. The present coupling was characterised by use of metal-free catalyst with excellent levels of regioselectivity, particularly for internal and conjugated styrenes. The utility of this γ-keto diester is further showcased by its transformation to other heterocyclic derivatives. Mechanistic studies supported evidence for a radical mechanism with a facile Kornblum-DeLaMare rearrangement.

Experimental Section

General procedure for metal free coupling of malonic esters with styrenes: To an oven dried pressure tube equipped with a stir bar were added 0.04 mmol of TBAI, 0.2 mmol of malonic ester **2**, 0.4 mmol of styrene **1**, 0.6 mmol of TMEDA and 1 mL of dry degassed acetonitrile solvent. The mixture was stirring for a while followed by the addition of 0.6 mmol of TBHP (5.5 M in decane), 4Å MS (2 wt %) and another 1 ml of dry degassed acetonitrile. Then the mixture was purged with nitrogen for a few minutes, capped with a teflon screw cap and heated at 120 °C for 3 h. After the reaction was completed as shown by TLC, the mixture was cooled to room temperature, quenched with $Na_2S_2O_3$ and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the corresponding γ-keto diesters **3-4**.

Acknowledgements

We are grateful to DST-INSPIRE (IFA 13-CH-90), SERB (ECR/2016/000270) and IIT(ISM) for financial support. SRC & IH thank IIT(ISM) Dhanbad and DST-INSPIRE for their research fellowships respectively. The authors also acknowledge SAIF-Panjab University, CIF-BIT, Mesra and CSS-IACS, Kolkata for providing NMR facilities.

Keywords: malonyl radical • oxidative coupling • ketodiester • metal-free conditions • TBAI/TBHP

[1] For selected reviews on radical cascade reactions, see: a) M. Albert, L. Fensterbank, E. Lacote, M. Malacria, *Top. Curr. Chem.* **2006**, *264*, 1; b) C. Chatgilialoglu, D. Crich, M. Komatsu, I. Ryu, *Chem. Rev.* **1999**, *99*, 1991; c) C.-P. Chuang, S.-F. Wang, *Tetrahedron Lett.* **1994**, *35*, 1283; d) X. Sun, J. Li, Y. Ni, D. Ren, Z. Hu, S. Yu, *Asian J. Org. Chem.* **2014**, *3*, 1317; e) D. Staveness, I. Bosque, C. R. J. Stephenson, *Acc. Chem. Res.* **2016**, *49*, 2295.

[2] For selected reviews, see: a) P. Renaud, *Chimia* **2001**, *55*, 1045; b) N. Corrigan, S. Shanmugam, J. Xu, C. Boyer, *Chem. Soc. Rev.* **2016**, *45*, 6165; For selected articles, see: c) J. Xu, A. Atme, A. F. M. Martins, K. Jung, C. Boyer, *Polym. Chem.* **2014**, *5*, 3321; d) L. A. Paquette, A. G. Schaefer, J. P. Springer, *Tetrahedron* **1987**, *43*, 5567; e) J. J. Davies, T. M. Krulle, J. W. Burton, *Org. Lett.* **2010**, *12*, 2738; f) J. Magolan, M. A. Kerr, *Org. Lett.* **2006**, *8*, 4561

[3] a) A. Citterio, R. Sebastiano, M. Nicolini, R. Santi, *Synlett* **1990**, *42*; b) T. Linker, B. Kersten, U. Linker, K. Peters, E.-M. Peters, H.-G. vonSchnering, *Synlett* **1996**, 468. c) F.-B. Li, X. You, G.-W. Wang, *Org. Lett.* **2010**, *12*, 4896; d) A. W. J. Logan, S. J. Sprague, R. W. Foster, L. B. Marx, V. Garzya, M. S. Hallside, A. L. Thompson, J. W. Burton, *Org. Lett.* **2014**, *16*, 4078 and references cited there in.

[4] a) B. Giese, *Angew. Chem. Int. Ed.* **1985**, *24*, 553; b) D. P. Curran, M.-H. Chen, E. Spletzer, C. M. Seong, C.-T. Chang, *J. Am. Chem. Soc.* **1989**, *111*, 8872; c) L. Cipolla, L. Liguori, F. Nicotra, G. Torri, E. Vismara, *Chem. Commun.* **1996**, 1253; d) E. Baciocchi, B. Giese, H. Farshchi, R. Ruzziconi, *J. Org. Chem.* **1990**, *55*, 5688; e) C. Wetter, K. Jantos, K. Woithe, A. Studer, *Org. Lett.* **2003**, *5*, 2899.

[5] a) J. Cheng, W. Li, Y. Duan, Y. Cheng, S. Yu, C. Zhu, *Org. Lett.* **2017**, *19*, 214; b) D. F. Reina, A. Ruffoni, Y. S. S. A. Ai-Faiyz, J. J. Douglas, N. S. Sheikh, D. Leonori, *ACS Catal.* **2017**, *7*, 4126; c) X. J. Wei, D. T. Yang, L. Wang, T. Song, L. Z. Wu, Q. Liu, *Org. Lett.* **2013**, *15*, 6054; d) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2012**, *134*, 8875; e) J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 368.

[6] a) C. Walling, E. S. Huyser, *Org. React.* **1963**, *13*, 91; b) M. Julia, *Acc. Chem. Res.* **1971**, *4*, 386. c) C. Wang, R.-H. Liu, M.-Q. Tian, X.-H. Hu, T.-P. Loh, *Org. Lett.* **2018**, *20*, 4032.

[7] For review, see: a) V. Nair, J. Mathew, J. Prabhakaran, *Chem. Soc. Rev.* **1997**, *26*, 127; b) V. Nair, A. Deepthi, *Tetrahedron* **2009**, *65*, 10745; For selected examples, see: c) E. Baciocchi, R. Ruzziconi, B. Giese, H. Farshchi, *J. Org. Chem.* **1990**, *55*, 5688; d) E. Baciocchi, R. Ruzziconi, D. D. Aka, *Tetrahedron Lett.* **1986**, *27*, 2763; e) A. Citterio, D. Fancelli, C. Finzi, L. Pesce, R. Santi, *J. Org. Chem.* **1989**, *54*, 2713.

[8] For selected reviews & book on $Mn(OAc)_3$ chemistry, see: a) Klein, W. J. *Organic Synthesis by Oxidation with Metal Compounds*, eds. Mijs, W. J. and de Jonge, C. R. H., Eds.; Plenum: New York, **1986**; pp 261; b) G. G. Melikyan, *Synthesis* **1993**, 833; c) J. Iqbal, B. Bhatia, N. K. Nayyar, *Chem. Rev.* **1994**, *94*, 519; d) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339; e) A. S. Demir, M. Emrullahoglu, *Curr. Org. Syn.* **2007**, *4*, 321.

[9] a) S. Bera, R. C. Samanta, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9622; b) M. V. Mey, A. Hatzelmann, I. J. V. Laan, G. J. Sterk, U. Thibaut, H. Timmerman, *J. Med. Chem.* **2001**, *44*, 2511; c) F. Cambeiro, S. Lopez, J. A. Varela, C. Saa, *Angew. Chem. Int. Ed.* **2014**, *53*, 5959; d) L. Lv, H. Xi, X. Bai, Z. Li, *Org. Lett.* **2015**, *17*, 4324; e) T. Matsumoto, S. Imai, T. Yamaguchi, M. Morihira, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 346.

[10] For recent reviews on radical difunctionalization of alkenes, see: a) X.-W. Lan, N.-X. Wang, Y. Xing, *Eur. J. Org. Chem.* **2017**, 5821; b) H. Yi, G. Zhang, H. Wang, Huang, Z. J. Wang, A. K. Singh, A. Lei, *Chem. Rev.* **2017**, *117*, 9016; For selected recent articles, see: c) S.-L. Zhang, X.-J.

Wang, Z.-L. Yu, *Org. Lett.* **2017**, *19*, 3139; d) M.-N. Zhang, M.-N. Zhao, M. Chen, Z.-H. Ren, Y-Y. Wang, Z.-H. Guan, *Chem. Commun.* **2016**, *52*, 6127; e) X.-W. Lan, N-X. Wang, C.-B. Bai, C.-L. Lan, T. Zhang, S.-L. Y. Chen Xing, *Org. Lett.* **2016**, *18*, 5986; f) N. Zhang, H. Yi, C. Xu, W. Deng, R. Wang, D. Peng, Z. Zeng, J. Xiang, *Org. Lett.* **2016**, *18*, 1780; g) M. Rössle, T. Werner, W. Frey, J. Christoffers, *Eur. J. Org. Chem.* **2005**, 5031; h) M. Rössle, T. Werner, A. Baro, W. Frey, J. Christoffers, *Angew. Chem. Int. Ed.* **2004**, *43*, 6547; i) S. Lu, L. Qi, Z. Li, *Asian J. Org. Chem.* **2017**, *6*, 313; j) X. Zheng, S. Lu, Z. Li, *Org. Lett.* **2013**, *15*, 5432.

[11] a) V. Nair, J. Mathew, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1881; b) V. Nair, J. Mathew, L. G. Nair, *Synth. Commun.* **1997,** *27*, 3053.

[12] V. Nair, A. Deepthi, *Chem. Rev.* **2007**, *107*, 1862.

[13] For reviews, see: a) R. Narayan, K. Matcha, A. P. Antonchick, *Chem. Eur. J.* **2015**, *21*, 14678; b) R. Samanta, K. Matcha, A. P. Antonchick, *Eur. J. Org. Chem.* **2013**, 5769; c) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; d) R. D. Richardson, T. Wirt, *Angew. Chem. Int. Ed.* **2006**, *45*, 4402.

[14] For an excellent review on TBAI/TBHP mediated oxidative transformation, see: a) X.-F. Wu, J.-L. Gong, X. Qi, *Org. Biomol. Chem.* **2014**, *12*, 5807 and references are therein; b) P. Finkbeiner, B. J. Nachtsheim, *Synthesis* **2013**, *45*, 979.

[15] See SI for the full optimization table.

[16] The ineffectiveness of inorganic bases might be due to the hydrolysis of starting malonate esters to acid in presence of water which was produced during the reaction (see the mechanism in scheme 4).

[17] a) T. W. Green, P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, (3rd ed.), John Wiley Sons, New York (**1999**); b) L. A. Cabell, J. S. McMurray, *Tetrahedron Lett.* **2002**, *43*, 2491; c) C. Song, H. Liu, M. Hong, Y. Liu, F. Jia, L. Sun, Z. Pan, J. Chang, *J. Org. Chem.* **2012**, *77*, 704; d) K. G. Lalwani, A. Sudalai, *Tetrahedron Lett.* **2016**, *57*, 2445.

[18] a) M. W. Pertino, C. Theoduloz, J. A. Rodriguez, T. Yanez, V. Lazo, G. *J.* Schmeda-Hirschmann, *Nat. Prod.* **2010**, *73*, 639; b) A. Jogi, A. Paju, T. Pehk, T. Kailas, A.-M. Muurisepp, M. Lopp, *Tetrahedron* **2009**, *65*, 2959; c) M. V. Mey, K. M. Bommele, H. Boss, A. Hatzelmann, M. V. Slingerland, G. J. Sterk, H. Timmerman, *J. Med. Chem.* **2003**, *46*, 2008; d) D. W. Robertson, N. D. J ones, J. H. Krushinski, G. D. Pollock, J. K. Swartzendruber, J. S. Hayes, *J. Med. Chem.* **1987**, *30*, 623.

[19] For an excellent review on dealkoxycarbonylation of malonate esters, see: A. P. Krapcho, *Synthesis* **1982**, 805.

[20] a) K. Miura, N. Fujisawa, H. Saito, D. Wang, A. Hosomi, *Org. Lett.* **2001**, *3*, 2591; b) B. Hu, H. Chen, Y. Liu, W. Dong, K. Ren, X. Xie, H. Xu, Z. Zhang, *Chem. Commun.* **2014**, *50*, 13547. c) D. Huang, M. Yan, W.-J. Zhao, Q. Shen, *Synth. Commun.* **2005**, *35*, 745.

[21] J. Chen, J. Li, W. Jiao, G. Wang, Y. Li, X. Cheng, G. Li, *J. Org. Chem.* **2016**, *81*, 9992 and the references cited there in.

[22] a) D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1976**, *9*, 13; b) H. Fischer, *Chem. Rev.* **2001**, *101*, 3581; c) A. Bravo, H.-R. Bjorsvik, F. Fontana, L. Liguori, F. Minisci, *J. Org. Chem.* **1997**, *62*, 3849; d) P. A. MacFaul, I. W. C. E. Arends, K. Ingold, D. D. M. Wayner, *J. Chem. Soc. Perkin Trans. 2* **1997**, 135; e) B. Schweitzer-Chaput, J. Demaerel, H. Engler, M. Klussmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 8737; f) C. Liu, D. Liu, A. Lei, *Acc. Chem. Res.* **2014**, *47*, 3459; g) L. Zhou, H. Yi, L. Zhu, X. Qi, H. Jiang, C. Liu, Y. Feng, Y. Lan, A. Lei, *Sci. Rep.* **2015**, *DOI: 10.1038/srep15934*; h) D. Liu, Y. Li, X. Qi, C. Liu, Y. Lan, A. Lei, *Org. Lett.* **2015**, *17*, 998; i) S. Wang, S. Tang, A. Lei, *Sci. bull.* **2018**, *DOI: 10.1016/j.scib.2018.06.004*.

[23] N. Kornblum, H. E. DeLaMare, *J. Am. Chem. Soc.* **1951**, *73*, 880.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

((Insert TOC Graphic here))

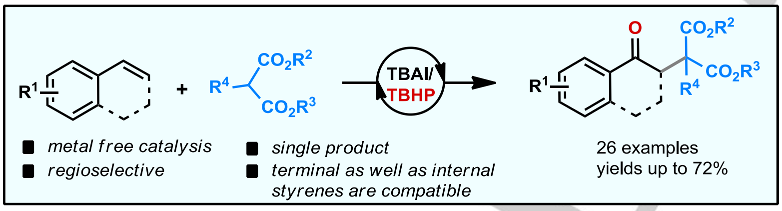
*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Layout 2:

COMMUNICATION



Metal-Free Malonyl: A Metal-free approach to the synthesis of γ-keto diester *via* oxidative radical coupling of styrenes with malonic esters has been developed. Key to the success of this process is the generation of malonyl radicals from malonic esters under organo-catalysis conditions with TBAI and TBHP.

*Soumyadeep Roy Chowdhury, Injamam Ul Hoque, and Soumitra Maity**

Page No. – Page No.

TBAI/TBHP-Promoted Generation of Malonyl Radicals: Oxidative Coupling with Styrenes Leads to γ–Keto Diesters