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Article

Photoredox-Catalyzed Radical Cyclization of Unactivated Alkene-Substituted β-Ketoesters Enabled Asymmetric Total Synthesis of Tricyclic Prostaglandin D_2 Metabolite Methyl Ester

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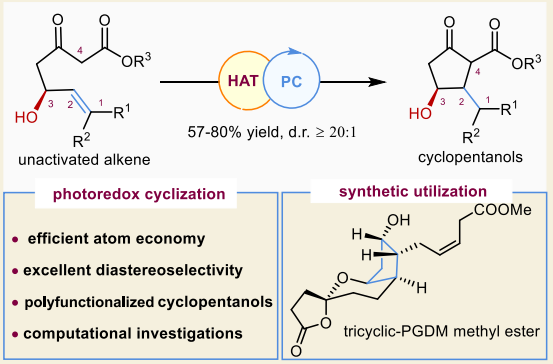
ABSTRACT: Regio- and stereoselective photoredox-catalyzed cyclizations of alkene-substituted β-ketoesters have been accomplished for the synthesis of polyfunctionalized cyclopentanones. This was achieved using 2,3,5,6-tetrakis(carbazol-9-yl)-1,4-dicyanobenzene (4CzTPN) and 2,4,6-triisopropyl-thiophenol as cocatalysts under illumination of a blue-light-emitting-diode at ambient temperature. The developed chemistry was successfully applied in the enantioselective total synthesis of the tricyclic prostaglandin D_2 metabolite (tricyclic-PGDM) methyl ester, which was completed in 9 steps with an overall yield of 7%.



KEYWORDS: *photoredox-catalyzed, cyclization, alkene-substituted β-ketoesters, tricyclic-PGDM methyl ester, asymmetric total synthesis*

Prostaglandins (PGs) are hormone-like lipid compounds comprising a five-membered cyclopentanol core (**A**; Figure 1a) bearing two aliphatic side chains. PGs play a remarkably diverse role in various physiological processes.[1] The identification and detection of both natural PGs and their stereoisomers are important for disease diagnosis, assessment of disease progression, and the development of therapeutics.[2] Accordingly, intensive effort has been devoted to their synthesis.[3] For instance, tricyclic-PGDM methyl ester (**4**) features a tricyclic spiro[cyclopenta[*b*]pyran-2,2′-furanone motif with four contiguous stereogenic centers. This molecule has been used as an indicator for PGD_2 overproduction,[4] highlighting its potential clinical application.[5] Thus, given its substantial clinical significance and intrinsic synthetic complexity, increasingly efficient chemical strategies for the total synthesis of tricyclic-PGDM methyl ester (**4**) have been established,[6] including a concise synthetic pathway recently reported by Dai et al.[7] Notwithstanding these advancements, an asymmetric approach to the synthesis of **4** has hitherto remained elusive.

The Snider-type radical cyclization represented the remarkable oxidative radical cyclization of C(sp^3)−H bond in β-ketoesters with unactivated olefins, which have garnered significant attention due to their ability to facilitate the construction of complex molecular architectures.[8] However, most of the successful examples usually depend on the use of a stoichiometric amount of metal oxidants, and efficient catalytic radical cyclization reactions under mild conditions without the use of noble metals presents a significant challenge.[9] Owing to its mild reaction conditions, broad functional group compatibility, and predictable reactivity, the past decade has seen stereocontrolled visible-light-induced photoredox catalysis emerging as a radical cyclization strategy to construct a wide array of highly functionalized bioactive and drug molecules.[10] Among the various methodologies in this domain, in 2022, Cannon et al.[11] documented the pioneering example for the construction of substituted cyclopentanones via a photoredox-catalyzed radical redox cyclization of styrene-substituted β-ketoester **B** in the presence of base (Figure 1b). The proposed mechanism involves the formation of an electron-deficient and resonance-stabilized radical species **C**, followed by intramolecular alkylation of the styrene to generate a stabilized benzylic radical **D**. This radical subsequently undergoes electron transfer (−1.1 V vs SCE)[12a] to form stabilized anion **E**, which is then protonated to yield product **F**. However, when the styrene is replaced with a nonactivated alkene, the cyclization reaction does not occur. We attributed this failure to the thermodynamic instability of radical **H**, which requires an agent with a higher reductive potency

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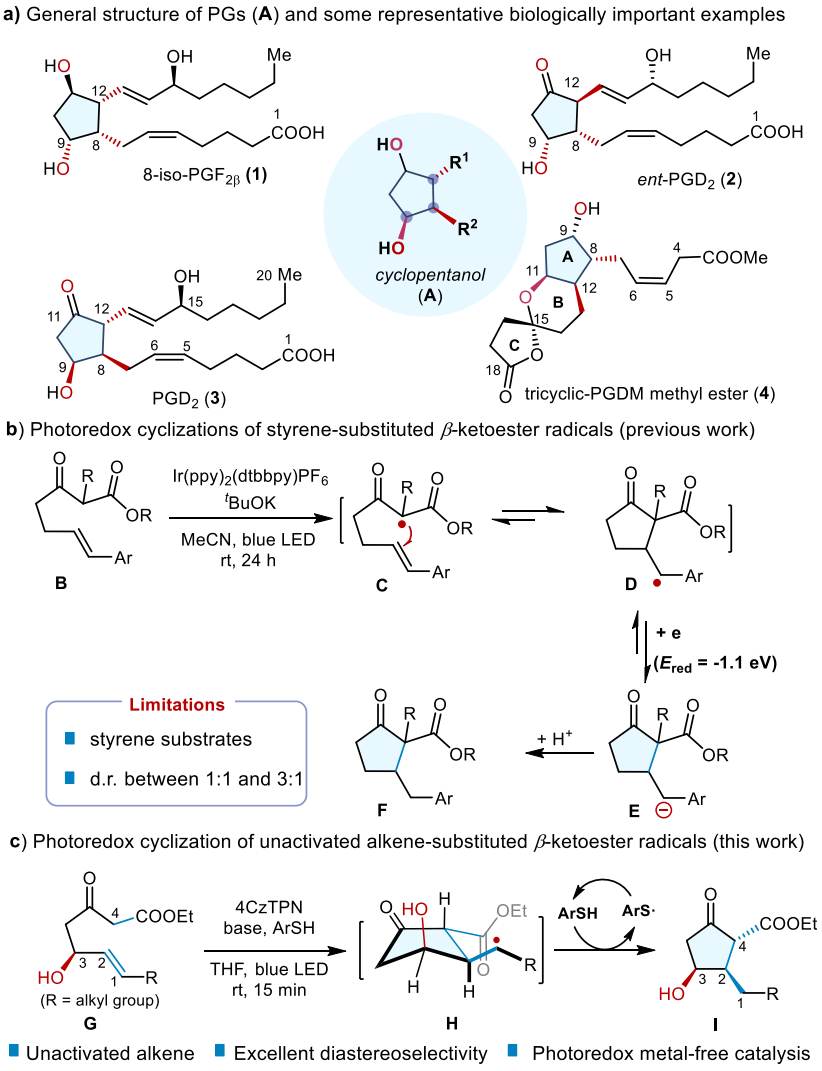

Figure 1. (a) General structure of PGs (**A**) and some representative biologically important examples. (b) Reported photoredox cyclizations of styrene-substituted β-ketoester radicals. (c) Research plan of photoredox cyclization of unactivated alkene-substituted β-ketoester radicals.

(exceeding −2.3 V vs SCE)[12a,b] to convert it into its corresponding carbon anion. In this report, we present the first stereoselective intramolecular hydroalkylation of unactivated alkene-substituted β-ketoesters under organo-photoredox catalysis to construct the key cyclopentanol ring skeleton. This strategy leverages the first asymmetric approach to the total synthesis of prostaglandin D_2 metabolite methyl ester (**4**).

Thiophenols are efficient hydrogen-atom-transfer (HAT) agents for alkyl radicals, with S−H-bond-dissociation enthalpies around 79 kcal/mol.[13] Therefore, we hypothesized that thiophenol could be used as a cocatalyst to convert radical **H** into product **I** (Figure 1c), with the in situ-generated stabilized ArS·radical being converted back into thiophenol in the presence of a photocatalyst.[14] Herein, cyclopentanone **I** could be delivered from alkene-substituted β-ketoester **G** with the successful implementation of this photoredox cyclization strategy using 2,4,6-triisopropyl thiophenol[15] (TRIPSH) as the HAT agent. Despite the high reactivity of the proposed HAT catalyst, which enables the intramolecular hydroalkylation of unactivated olefins, several challenges remain in achieving the stereoselectivity of this radical cyclization process. These challenges include: (1) determining whether the stereo-directing ability of the pendant allyl alcohol in **G**[16] can help enforce a reactive conformation during the radical cyclization step (**G** → **H**); and (2) establishing whether the desired stereochemistry, particularly that for the contiguous C8, C11, and C12 carbon centers, could be correctly formed in the resulting cyclopentanol. These stereochemical elements are crucial for the synthesis of **4**.

Our research commenced with a systematic investigation of the proposed photoredox-catalyzed cyclization of β-ketoester **5a** in the presence of thiophenol and Ir-based blue phosphorescent catalysts[17] such as $[Ir(dtbbpy)(ppy)_2]PF_6$,[11] $Ir(ppy)_3$,[18] and $[Ir(dtbbpy)(dF(CH_3)\text{-}ppy)_2]PF_6$[19] under reaction conditions reported in the literature. However, none of these catalysts provided satisfactory results for the formation of the cyclized product **6a** (see Supporting Information for details).

After intensive experimentation, we found that the desired 5-*exo* cyclized product **6a** could be obtained in 44% yield as a single diastereomer (dr ≥ 20:1, ^{1}H NMR analysis) when the reaction was carried out in the presence of a catalytic amount of photocatalyst 4CzTPN,[20] thiophenol,[21] and K_3PO_4[22] as a Brønsted base under irradiation by a blue LED (20 W) at room temperature for 15 min (Table 1, entry 1). Encouraged

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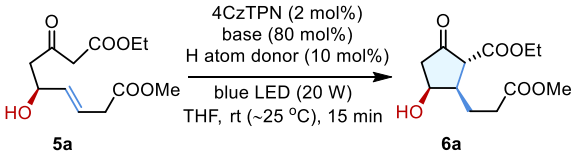
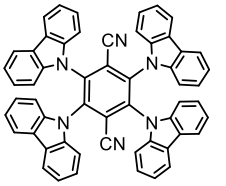
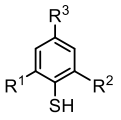
Table 1. Optimization of Reaction Conditions[a]



entry	base	solvent	H atom donor	yield (%)	d.r.[c]
1	K_3PO_4	THF	thiophenol	44	≥20:1
2	K_3PO_4	THF	4-methylthiophenol	51	≥20:1
3	K_3PO_4	THF	4-cyanothiophenol	8	–
4	K_3PO_4	THF	4-trifluoromethylthiophenol	5	-
5	K_3PO_4	THF	2,6-dimethylthiophenol	58	≥20:1
6	K_3PO_4	THF	2,4,6-trimethylthiophenol	61	≥20:1
7	K_3PO_4	THF	TRIPSH	68[b]	≥20:1
8	K_3PO_4	THF	*n*-butanethiol	36	≥20:1
9	K_3PO_4	THF	*t*-butylthiol	35	≥20:1
10	K_3PO_4	THF	—	0	-



4CzTPN



$R^1 = R^2 = R^3$ = H, thiophenol
$R^1 = R^2$ = H, R^3 = Me, 4-methylthiophenol
$R^1 = R^2$ = H, R^3 = CN, 4-cyanothiophenol
$R^1 = R^2$ = H, $R^3 = CF_3$, 4-trifluoromethylthiophenol
$R^1 = R^2$ = Me, R^3 = H, 2,6-dimethylthiophenol
$R^1 = R^2 = R^3$ = Me, 2,4,6-trimethylthiophenol
$R^1 = R^2 = R^3 = {}^i$Pr, TRIPSH

[a]Reaction conditions: all reactions were carried out with **5a** (0.2 mmol), 4CzTPN (2 mol %), base (80 mol %), H atom donor (10 mol %), and solvent (20 mL) unless otherwise stated. The reactions were irradiated with a 20 W blue LED under argon atmosphere for 15 min. [b]Isolated yield. [c]Diastereomeric ratios (d.r.) were determined by ^{1}H NMR analysis.

by this result, we investigated the electronic effect of the thiophenol substituents on the cyclization of **5a** using 4-methyl-, 4-cyano-, and 4-trifluoromethyl-substituted thiophenols as HAT agents. 4-Methylthiophenol gave the desired cyclized product **6a** in 51% yield (entry 2) while thiophenols substituted with electron-withdrawing groups[23] (such as 4-cyano and 4-trifluoromethyl moieties) gave cyclized product **6a** in low yields (entries 3 and 4). We next explored steric effects using 2,4-dimethylthiophenol, 2,4,6-trimethylthiophenol, and TRIPSH as the HAT agent. To our delight, the use of TRIPSH afforded the desired product in 68% yield (entries 4−7), indicating that steric effects play a critical role in the cyclization of **5a**. We also explored the use of alkyl thiols as HAT agents in this cyclization; however, cyclized product **6a** was obtained in lower yields (entries 8 and 9). Control experiments indicated that a thiolic HAT agent is essential for this cyclization reaction (entry 10). Subsequently, we evaluated the effects of Brønsted base, solvent, and temperature. However, no enhancement in the yield of **6a** was observed (For full screening, see the Supporting Information).

After extensive experimentation, it was discovered that alkene-substituted ketoester **5a** could be regio- and stereoselectively cyclized using catalytic quantities of 4CzTPN and TRIPSH, along with K_3PO_4 as the base, in THF under LED irradiation at ambient temperature for 15 min, affording the desired product **6a** in 68% yield.

To assess the generality of this procedure, other alkene-substituted ketoesters (**5b**−**5o**) were prepared and cyclized. The experimental results are summarized in Figure 2.

Remarkably, all the substrates provided satisfactory yields under the optimized conditions, with efficient atom economy[24] and complete reaction progress. The structure of **6h** was confirmed by X-ray crystallographic analysis of its derivative (see Supporting Information for details).[25] Interestingly, styrene-based *β*-ketoester **5i** and substrates with a longer linker, namely **5j** (*m* = 2) and **5k** (*m* = 3), were also cyclized to give the corresponding products **6i**, **6j**, and **6k** in good yields (Figure 2, entries 8−10). This demonstrates that this methodology represents a versatile approach for the stereoselective synthesis of polyfunctionalized cyclic ketones. Moreover, the trisubstituted alkenes, i.e., **5l**, **5m**, **5n**, and **5o**, gave the cyclization products **6l**, **6m**, **6n**, and **6o** with opposite stereochemistries at C2 and C3 (Figure 2, entries 11−14).

Several key aspects of this reaction system are noteworthy. (1) Both terminal and substituted alkenes[26] yield their corresponding radical cyclized products in good yields (2) all the reactions give the cyclized product in a diastereoselective manner; (3) the diastereoselectivity of the cyclization reaction is reversed when 1,1-disubstituted terminal alkenes are employed; and (4) the C2, C3, and C4 stereogenic centers are consistent with those in the resulting PGs, highlighting the potential of this system for the synthesis of tricyclic-PGDM methyl ester (**4**). The current limitations of this transformation

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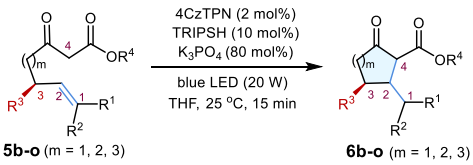

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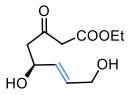
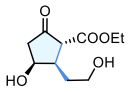
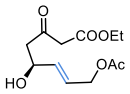
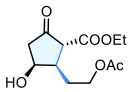
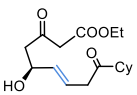
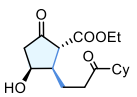
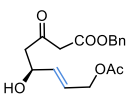
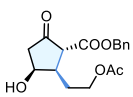
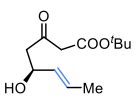
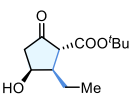
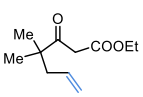
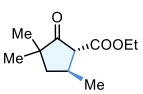
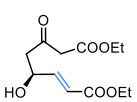
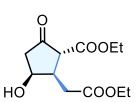
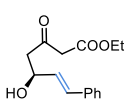
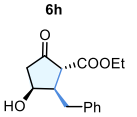
1	 5b	 6b	63%
2	 5c	 6c	62%
3	 5d	 6d	61%
4	 5e	 6e	67%
5	 5f	 6f	60%
6	 5g	 6g	71%
7	 5h	 6h	58%[c]
8	 5i	 6i	61%[d]

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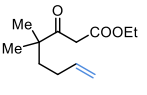
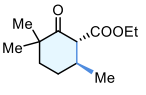
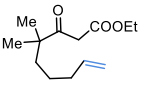
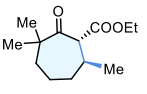
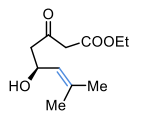
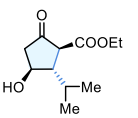
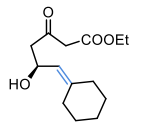
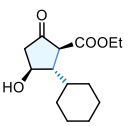
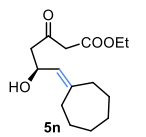
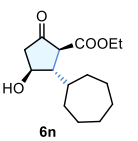
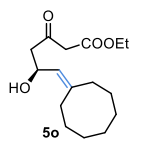
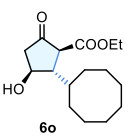
9	 5j	 6j	79%
10	 5k	 6k	75%
11	 5l	 6l	75%
12	 5m	 6m	63%
13	 5n	 6n	65%
14	 5o	 6o	57%

unsuccessful substrates

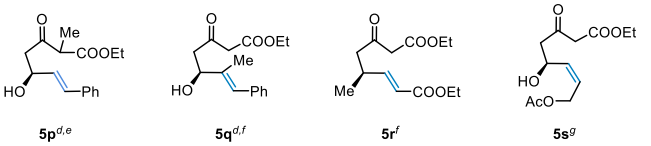


Figure 2. Substrate scope of photoredox-catalyzed radical cyclization of alkene-substituted β-ketoesters. [a]Reaction conditions: alkene-substituted ketoester (0.2 mmol), 4CzTPN (2 mol %), K_3PO_4 (80 mol %), TRIPSH (10 mol %), and THF (20 mL) in the presence of 20 W blue LED at 25 °C under argon unless otherwise stated. [b]Isolated yield, d.r. ≥ 20:1 unless otherwise specified. [c]Reaction irradiated for 45 min. [d]Reaction irradiated for 3 h. [e]The desired product was not detected, and starting materials remained unreacted. [f]Complex reaction mixture was observed. [g]The starting material was decomposed.

were shown (Figure 2). The failure of α-substituted β-keto ester **5p** was presumably due to the limitation of generating an enol anion under the basic condition of K_3PO_4.[27] The radical cyclization reaction with trisubstituted alkene **5q** did not proceed well, giving complicated mixture. The C3-methyl-substituted substrate **5r** failed to deliver the desired product, which suggested that the hydroxy group at C3 might play an important role not only in determining the stereoselectivity but also in the success of the cyclization reaction. Meanwhile, the *E*-alkene **5s** was decomposed intermediately under the standard reaction conditions.

To gain more insight into the stereoselective formation of cyclopentanones in this system, we performed density functional theory (DFT) calculations using **5a** as the model reactant. As depicted in Figure 3a, the relative free energy of **TS-1-*syn-anti*** is 1.5 kcal/mol lower than that of **TS-1-*anti-anti***, indicating that the ***syn-anti*** configuration would be preferential. Geometric analysis revealed that the hydroxyl group prefers to occupy an equatorial position in **TS-1-*anti-anti***, prompting the allyl alcohol to adopt the *anti*-conformation.[28] Consequently, the existent additional hyperconjugative interaction (σ_{C-O}^*/π)[29] would render the reacting

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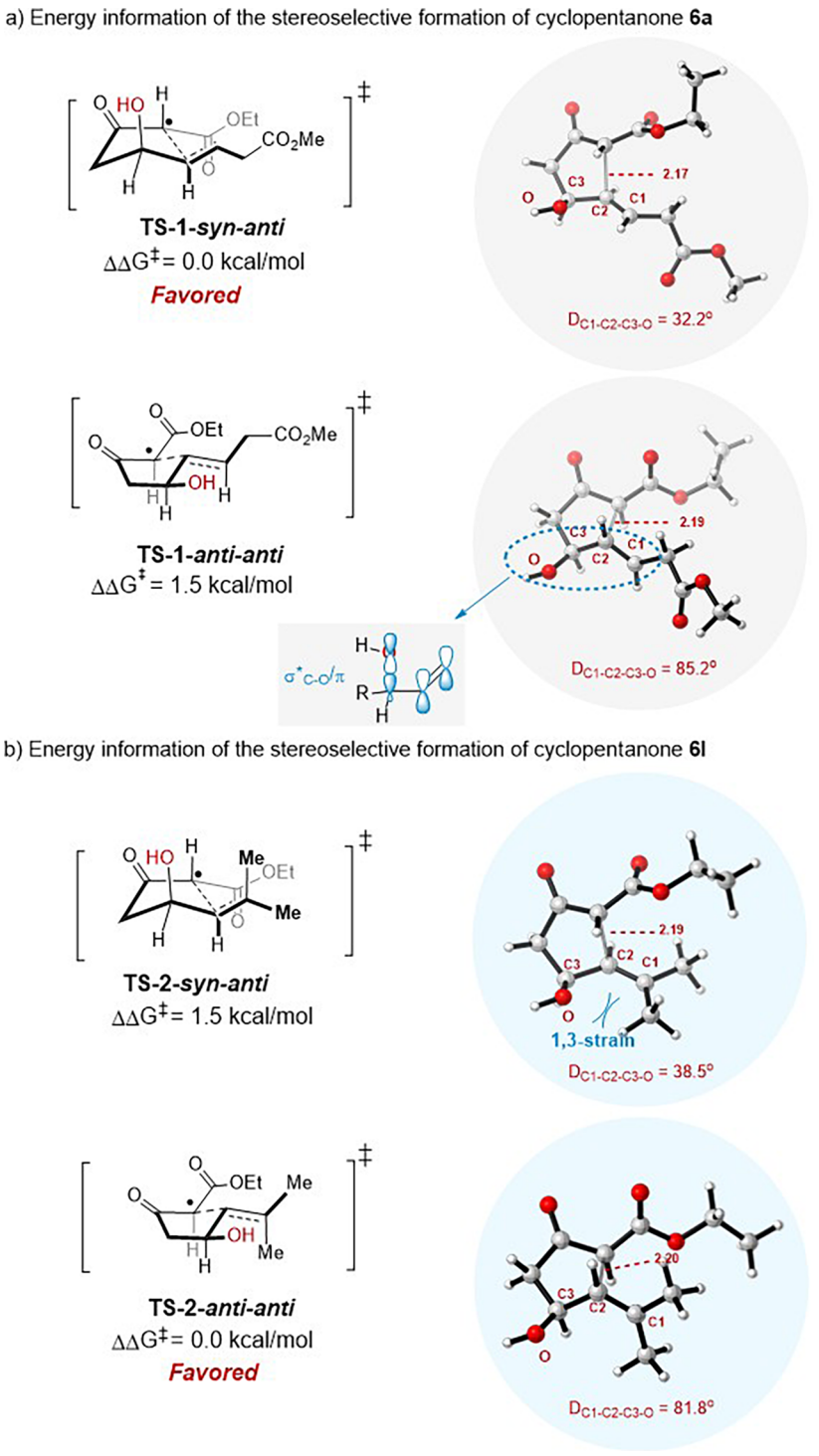

Figure 3. Results of DFT investigation on the stereoselectivity of the radical cyclization process. The relative free energies given in kcal/mol are calculated at the M06/6-311++G**//B3LYP-D3/6-31+G* level in THF (SMD solvation model). Bond lengths are given in Å.

C═C bond electron-deficient in **TS-1-*anti-anti***, which results in high energy for its electrophilic radical addition.[30] When reactant **5l** was employed, the 1,3-strain between the hydroxyl and methyl group caused the relative free energy of **TS-2-*syn-anti*** to be 1.5 kcal/mol higher than that of **TS-2-*anti-anti***, even in the absence of the corresponding σ_{C-O}^*/π interaction in **TS-2-*syn-anti*** (Figure 3b). This suggests that steric hindrance is largely responsible for the reversal of stereoselectivity in the reaction of **5l**.

To verify the feasibility of this synthetic methodology, we conducted the enantioselective total synthesis of tricyclic-PGDM methyl ester (**4**) (Scheme 1). Enantioselective synthesis of the key intermediate **11** was accomplished by reaction of Chan's diene **7**, synthesized from commercially available ethyl acetoacetate in two steps,[31] with (*E*)-but-2-enal (**8**) in the presence of LiCl and a catalytic amount of Ti(O*i*-Pr)$_4$/(*S*)-BINOL complex[32] in THF at room temperature followed by the TMS deprotection with pyridinium 4-toluenesulfonate (PPTS). The resultant alcohol **9** (e.r.

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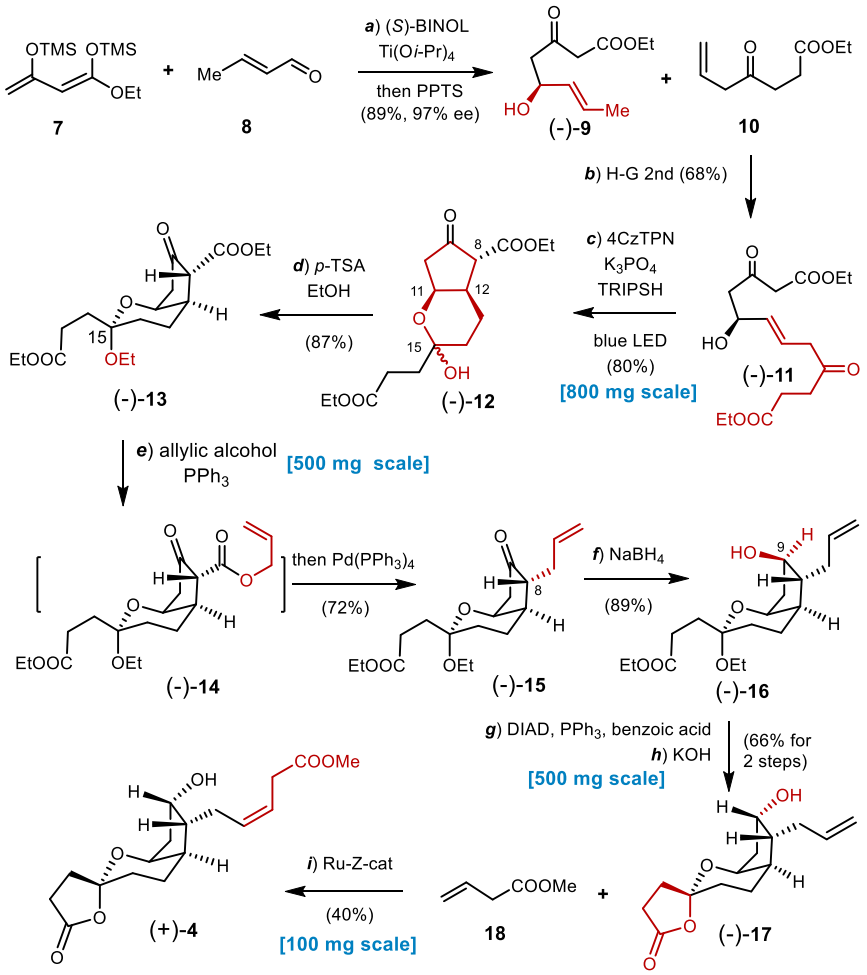
Scheme 1. Total Synthesis of Tricyclic-PGDM Methyl Ester (4)[a]



[a]Reagents and conditions: (*a*) **7** (1.00 equiv), **8** (3.00 equiv), (*S*)-BINOL (0.06 equiv), Ti(O*i*-Pr)$_4$ (0.06 equiv), LiCl (0.24 equiv), THF, rt, 14 h; then PPTS, 0 °C, 2 h, 89%; (*b*) **9** (1.00 equiv), **10** (4.00 equiv), H-G second catalyst (0.05 equiv), 60 °C, 20 h, 68% ($E/Z \geq 20{:}1$); (*c*) 4CzTPN (0.02 equiv), K_3PO_4 (0.80 equiv), TRIPSH (0.10 equiv), blue LED (20 W), 25 °C, 30 min, 80%; (*d*) *p*-TSA (0.10 equiv), 4 Å molecular sieves, EtOH, rt, 5 h, 87%; (*e*) allylic alcohol (20.00 equiv), PPh_3 (0.20 equiv), PhMe, 128 °C, 2 h; then $Pd(PPh_3)_4$, PhMe, rt, 12 h, 72%; (*f*) $NaBH_4$ (0.30 equiv), EtOH, 0 °C, 5 h, 89%; (*g*) DIAD (3.00 equiv), PPh_3 (3.10 equiv), benzoic acid (1.10 equiv), THF, rt, 12 h; (*h*) KOH (5.0 M), MeOH, 45 °C, 4 h, 66% for 2 steps; (*i*) Ru-*Z*-cat (0.20 equiv), **18** (8.00 equiv), DCE, 40 °C, 12 h, 40% (E/Z = 1:16). Abbreviations: (*S*)-BINOL = (*S*)-1,1′-bi-2-naphthol; DIAD = diisopropyl azodicarboxylate; Ru-*Z*-cat = 1-[Rel-(2*R*,5*R*,7*R*)-adamantane-2,1-diyl][3-(2,4,6-trimethylpheny-l)]-2-imidazolidinylylidene](nitrato-*O*,*O*′)(*o*-isopropoxybenzylid-ene) ruthenium(II).

98.8:1.2, HPLC analysis) was then treated with a cross-metathesis reaction with olefin **10**[33] to give ketoester **11** in 60% yield ($E/Z \geq 20{:}1$, ^{1}H NMR analysis) for the two steps. Ketoester **11** was then cyclized under the optimized photoredox-catalysis conditions to afford **12** in 80% yield as a pair of diastereomers (at C15) in a ratio of 1.0/1.1 (^{1}H NMR analysis). Thus, upon treatment of **12** with *p*-toluenesulfonic acid (*p*-TSA) in ethanol, ketal **13** was obtained in 87% yield (e.r. 98.6:1.4, HPLC analysis) as a single diastereomer. To install the C8 stereogenic center in **15**, ketal **13** was treated with allylic alcohol in the presence of a catalytic amount of PPh_3,[34] and the resultant ester was then subjected to Pd-catalyzed decarboxylative allylation[35] to give product **15** in 72% yield in a one-pot fashion.

To complete the total synthesis, we envisioned that chemo- and diastereoselective reduction of the ketone could achieve the introduction of the hydroxyl group at C9 in a single step. However, the ketone in **15** is embedded within the inherent concave face (which is more sterically hindered than its convex face). Accordingly, commonly used reductants, such as ^{t}BuNH$_2$·BH$_3$, DIBAL-H, and LiAlH(O^{t}Bu)$_3$, provided product **16** with undesired C9 stereochemistry. Therefore, the ketone motif in **15** was first reduced with $NaBH_4$, then the newly generated chiral alcohol moiety at the C9 position in **16** was inverted by a Mitsunobu reaction followed by lactonization to afford **17** in 59% yield in three steps. Finally, the terminal alkene in **17** underwent a Ru-catalyzed *Z*-selective cross-metathesis reaction with olefin **18** to give **4** in 40% yield (E/Z = 1:16, ^{1}H NMR analysis).[7,36]

In conclusion, we have developed a general method for regio- and stereoselective synthesis of polyfunctionalized cyclopentanones from *β*-ketoester-linked alkenes via photoredox-catalyzed oxidative radical cyclization in the presence of cophotocatalysts 4CzTPN and TRIPSH under blue-LED irradiation at room temperature. A key finding of our study is the identification of TRIPSH as an effective catalytic mediator of HAT to the cyclized radical of the substrate. The stereoselectivity of this radical cyclization reaction is mainly

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dependent on the stereoelectronic and steric effects of the pendant allyl alcohol. The developed chemistry has been successfully applied to the asymmetric total synthesis of tricyclic-PGDM methyl ester (**4**) in 9 steps with an overall yield of 7% from the readily available Chan's diene **7**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c01268.

Experimental procedures and spectral data for all new compounds (PDF)

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Author Contributions

[‖]M.X. and Q.S. contributed equally. M.X. and Q.S. discovered and developed the reaction, designed the experiments. M.X., Q.S., L.P., and J.H. ran the experiments. Z.W. and L.Z. conducted the computations. L.Z. provided guidance on the computations. Z.Y. and J.H. directed the project. L.Z., Z.Y. and J.H. wrote the manuscript. CRediT: **Miao Xiao** conceptualization, data curation, formal analysis, investigation, methodology, writing - review & editing; **Qiaoli Shang** conceptualization, data curation, formal analysis, investigation, methodology, writing - review & editing; **Liu-Yang Pu** formal analysis, visualization, writing - review & editing; **Zhe-Yuan Wang** investigation, writing - review & editing; **Lei Zhu** formal analysis, investigation, writing - review & editing; **Zhen Yang** conceptualization, project administration, writing - review & editing; **Jun Huang** conceptualization, funding acquisition, project administration, writing - original draft, writing - review & editing.

Notes

The authors declare no competing financial interest.

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