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Regio- and Stereoselective Synthesis of (*Z*)-3-Ylidenephthalides via $H_3PMo_{12}O_{40}$-Catalyzed Cyclization of 2-Acylbenzoic Acids with Benzylic Alcohols

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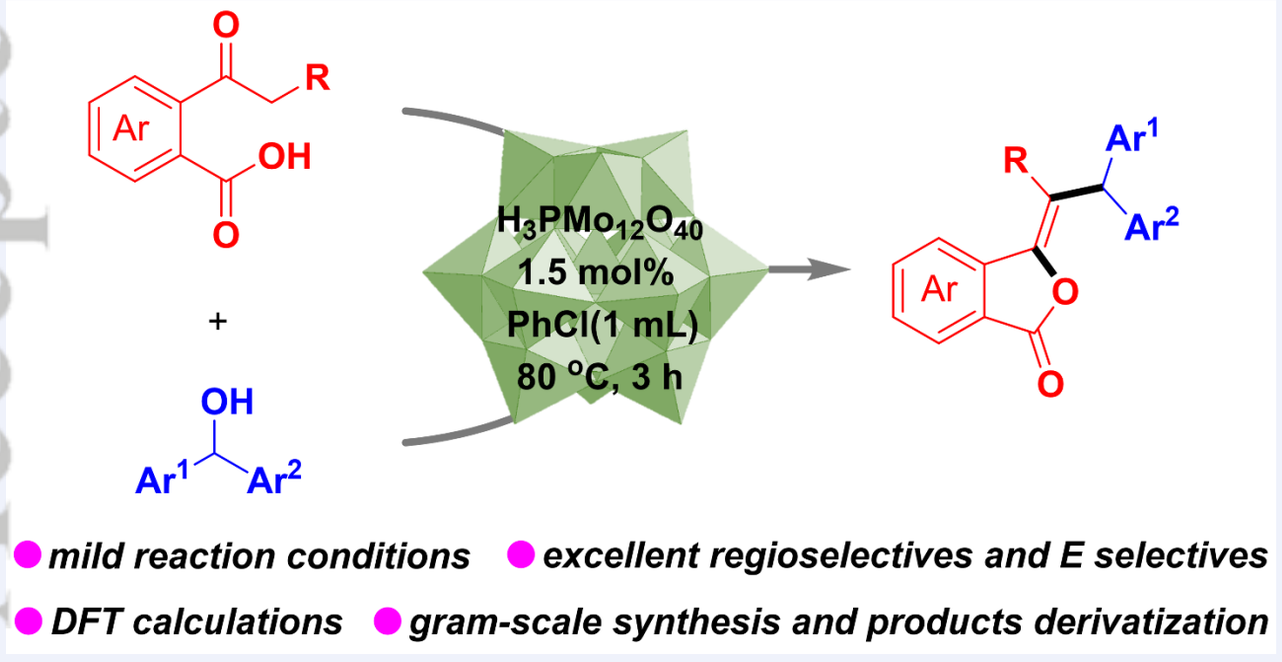
Keywords

Phosphomolybdic acid | Regio- and stereoselective | (*Z*)-3-ylidenephthalides | 2-Acylbenzoic acids | Benzylic alcohols

Main observation and conclusion

We report an exclusively tandem C–O and C–C bond forming beyond the esterification and cyclization reaction of 2-acylbenzoic acids with alcohols to regio- and stereoselective synthesis the (*Z*)-3-ylidenephthalides. The reaction uses the nontoxic, inexpensive $H_3PMo_{12}O_{40}$ as catalyst and produces water as the sole by-product, making the reaction environmentally benign and sustainable. Moreover, this reaction features an eco-friendly reaction conditions, facile scalability, and easy derivatization of the products to drugs and bioactive compounds. The mechanism studies and DFT calculations reveal that the appropriate acid catalyst is the key to the selectivity of this transformation.

Comprehensive Graphic Content



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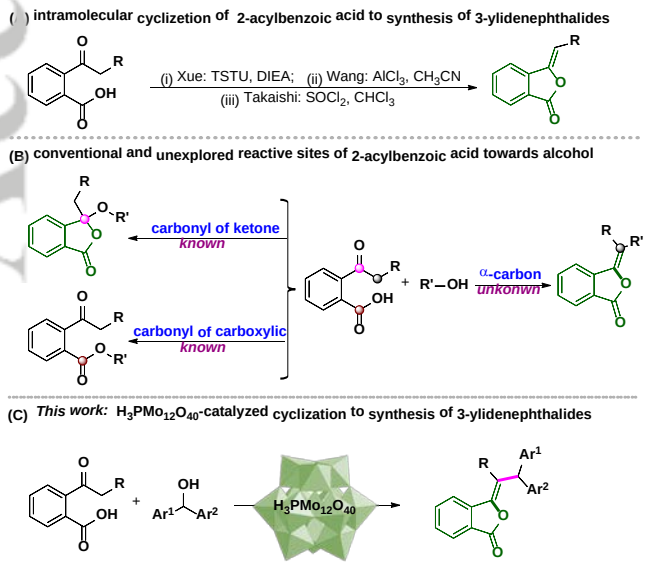
Background and Originality Content

3-Ylidenephthalides and polyheterocycles containing a isobenzofuran-1(*3H*)-ones are common motifs in drugs, natural products, wide-ranging biological activities and important intermediates to further build other bioactive heterocyclic compounds in orgnic synthesis.[1] For example, the Chinese angelica ingredient 3-butylidenephthalide exhibit antidiabetic, antispasmodic, anticoagulant, and antiproliferative activities.[1c] Multiple methods to generate such structures have been disclosed.[2] The main methods of intermolecular cyclization methods include the modified Perkin or Julia reaction with phthalic anhydride,[3] transition-metal-catalyzed cyclization of benzoic acid derivatives with alkenes or alkynes and the CO insertion-annulation reactions.[4] An alternative strategy is the intramolecular cyclization reaction such as the cyclization of 2-allyl or 2-alkenyl benzoic acid derivatives and the annulation of 2-alkynylbenzaldehydes.[5] Although these methods provided various strategies for the preparation of 3-ylidenephthalides, they still have limitations including harsh reaction conditions, expensive catalysts, ligands and side products.[6]

The cyclization of 2-acylbenzoic acids is a convenient method for the direct and atom-economical synthesis of 3-ylidenephthalides. Some catalytic systems have been developed in this area such as $SOCl_2/CHCl_3$ system, TSTU/DIEA system and $AlCl_3/CH_3CN$ system.[7] However, the above methods need toxic or expensive reagents and the intramolecular strategy result in the limitation of products, only the monosubstituted of terminal double bond products can be obtained (Scheme 1A). Meanwhile, 2-acylbenzoic acids are recognized as the crucial substrates coupled with nucleophile such as aniline or alcohol in the intramolecular cyclization reaction, but the corresponding products were not 3-ylidenephthalides.[8] It is well know that the electrophilic nature of carbonyl group permits easily coupling with nucleophile, which leads to the formation of other products. In principle, the reactions between 2-acylbenzoic acids and alcohols take place at the carbonyl site of ketone or carboxyl giving the 3-substituted phthalides or 2-acylbenzoate product (Scheme 1B).[9] However, it's still a challenge that 2-acylbenzoic acids react with alcohols at the α-carbon site of ketone to produce 3-ylidenephthalides. Herein, we envision to fill this gap by reporting our new results on the direct cyclization of 2-acylbenzoic acids with benzylic alcohols producing 3-ylidenephthalides (Scheme 1C).

Scheme 1 Varied reaction patterns between 2-acylbenzoic acid and alcohol

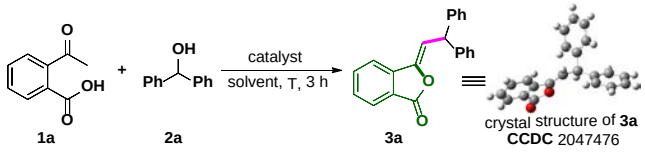


Environmentally benign and inexpensive polyoxometalates (POMs) are demonstrated to be practical and selective catalysts for the coupling and cyclization reaction.[10] In this protocol, we believe that the benzylic alcohol is protonated by phosphomolybdic acid ($H_3PMo_{12}O_{40}$) to generate a stable benzyl cation,[11] which avoiding the addition reaction with carbonyl group. Furthermore, the side products such as phthalides or ester are hard to exist because of the highly acidic of reaction condition.

Results and Discussion

We initiated our studies using 2-acetylbenzoic acid (**1a**) and diphenylmethanol (**2a**) as the model substrates to vary the reaction parameters (Table 1). After the extensive screening (see Supporting Information Tables S1-S6 for more details), we found that the treatment of substrates in chlorobenzene (PhCl) at 80 °C for 3 h in the presence of a catalytic amount of $H_3PMo_{12}O_{40}$ resulted in the formation of product **3a** in 93% yield (Table 1, entry 3). The structure of **3a** was conformed by crystal and the *Z*-selectivity may be due to the Z-configuration of product is more stable than its E-configuration and steric hindrance effect. Decreased yields were obtained with other Keggin-type POMs, e.g., $H_4SiW_{12}O_{40}$ and $H_3PW_{12}O_{40}$ as the catalyst, which may be due to the softest heteropoly anion of $H_3PMo_{12}O_{40}$ can stabilize the reaction intermediate (entries 1-3).[11] Other Bronsted acid like *p*-TSA did not improve the yield compared to the POMs (entry 4). Two representative Lewis acids, $FeCl_3$ and $Cu(OTf)_2$, were tested as catalysts under the same conditions and did not form any desired product (entries 5 and 6). No product was obtained in the absence of catalyst (entry 7). Solvent screening results seem indicated that nonpolar solvents are beneficial to give a better yield than polar solvents (entries 8-13). Low temperature lead to a lower yield and increasing temperature did not improve the yield (entry 14 and 15).

Table 1 Optimization of reaction conditions.[a]

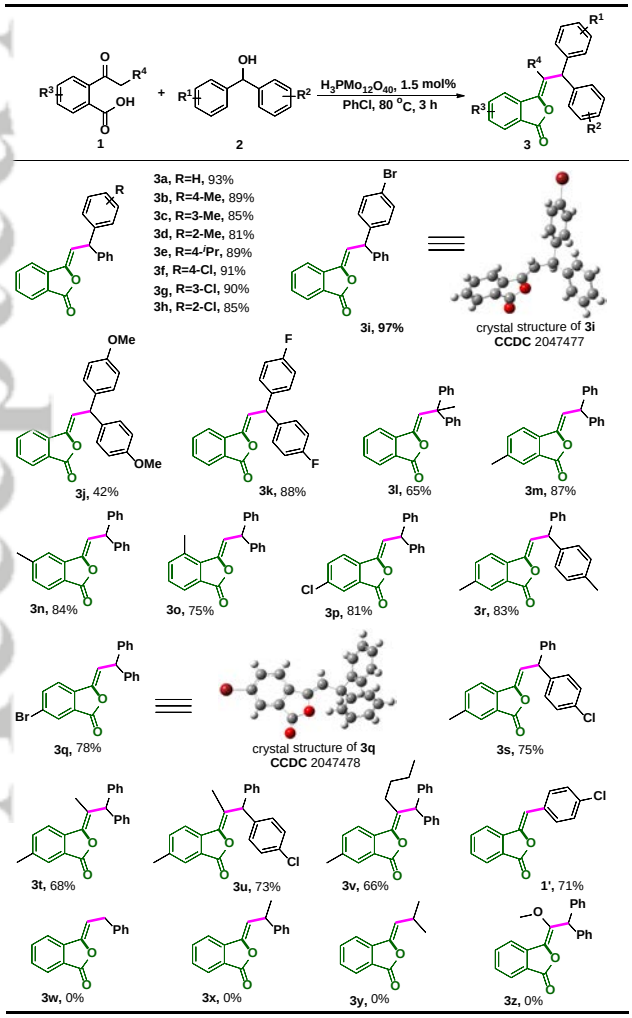


Entry	Catalyst (mol %)	Solvent	T (°C)	Yield (%)[b]
1	$H_3PW_{12}O_{40}$ (1.5)	PhCl	80	71
2	$H_4SiW_{12}O_{40}$ (1.5)	PhCl	80	72
3	$H_3PMo_{12}O_{40}$ (1.5)	PhCl	80	93
4	*p*-TSA (10)	PhCl	80	46
5	$FeCl_3$ (10)	PhCl	80	0
6	$Cu(OTf)_2$ (10)	PhCl	80	0
7	—	PhCl	80	0
8	$H_3PMo_{12}O_{40}$ (1.5)	H_2O	80	11
9	$H_3PMo_{12}O_{40}$ (1.5)	DCE	80	67
10	$H_3PMo_{12}O_{40}$ (1.5)	Toluene	80	69
11	$H_3PMo_{12}O_{40}$ (1.5)	Benzene	80	61
12	$H_3PMo_{12}O_{40}$ (1.5)	CH_3CN	80	19
13	$H_3PMo_{12}O_{40}$ (1.5)	CH_3NO_2	80	49
14	$H_3PMo_{12}O_{40}$ (1.5)	PhCl	70	83
15	$H_3PMo_{12}O_{40}$ (1.5)	PhCl	90	93

[a] Reaction conditions: 2-acetylbenzoic acid (**1a**, 0.3 mmol), diphenylmethanol (**2a**, 0.2 mmol), solvent (1.0 mL), catalysis for 3 h. [b] The yields determined by GC with biphenyl as the internal standard.

Having identified optimized conditions for substrates **1a** and **2a**, we next explored the scope of this reaction. A range of benzylic alcohol derivatives in the cyclization reaction with 2-acetylbenzoic acid (**1a**) as the standard substrate was examined.[12] As shown in Table 2, diphenylmethanols substituted with electron-donating (Me, ^{i}Pr, OMe) or electron-withdrawing groups (F, Cl, Br) smoothly underwent cyclization to give the desired products **3b**-**3k**. The reactivity of this reaction was slightly influenced by the electronic properties of the aryl rings. Diphenylmethanols with electron-donating groups afforded lower yields of the corresponding products (**3b**-**3d**) than those with electron-withdrawing groups (**3f**-**3i**). Furthermore, diphenylmethanols bearing the same substituents at different positions also had little influence on the efficiency of this transformation. For example, the Me or Cl substituent at *ortho*-position of phenyl rings gave lower yield than *meta*-/*para*-position (**3b**/**3c**/**3d** or **3f**/**3g**/**3h**). In the case of tertiary alcohol, the corresponding product **3l** was obtained in a yield of 65%. The substrate scope of 2-acetylbenzoic acids were also tested with diphenylmethanol as substrates. 2-Acylbenzoic acids with electron-donating and electron-withdrawing functional groups all reacted smoothly with diphenylmethanols to generate the desired products in good yields (**3m**-**3s**). To expand the substrate scope of this transformation, we examined the different 2-acyl-substitutents. 2-Propionylbenzoic acid and 2-caproylbenzoic acid

Table 2 Substrate scope.[a, b]

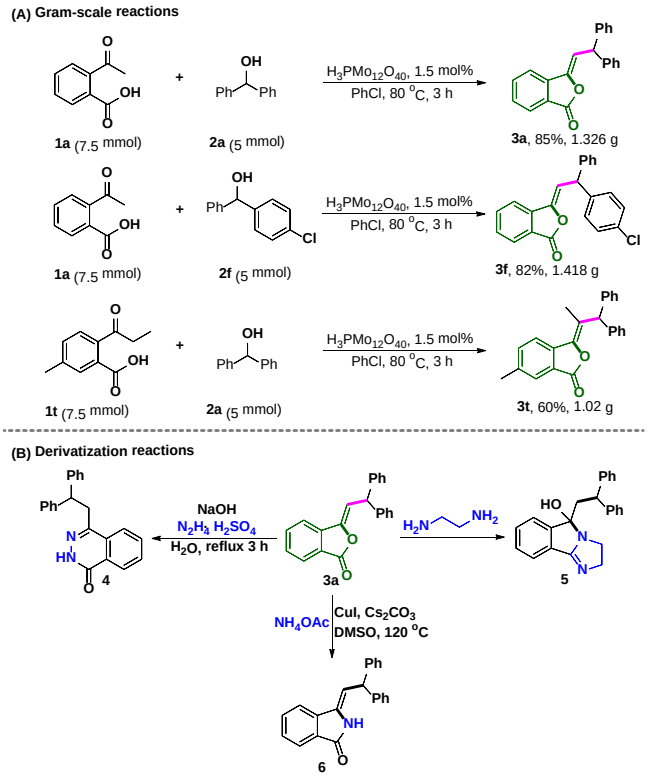


[a] Reaction conditions: 2-acylbenzoic acid (**1**, 0.3 mmol), diphenylmethanol (**2**, 0.2 mmol), PhCl (1.0 mL), $H_3PMo_{12}O_{40}$ (1.5 mol %), 80 °C for 3 h. [b] Isolated yield.

were cyclized well to give the desired products **3t**, **3u** and **3v** in good yields with different benzylic alcohols. It was noted that the 2-phenylacetyl substrate underwent the cyclization process to provide 3-ylidenephthalide **1'** rather than the expected product, which may be due to the steric hindrance effect of the benzene ring substituent in C=C bond. Unfortunately, simple alcohol and 2-(2-methoxyacetyl)benzoic acid couldn't convert to the desired products under the standard conditions (**3w**-**3z**).

After developing the methodology, we further demonstrated its utility by the gram-scale synthesis and derivatization reactions. The product **3a**, **3f** and **3t** could be produced without modifying the standard conditions in 85%, 82% and 60% yields on a 5 mmol scale, respectively (Scheme 2A). The 3-ylidenephthalide skeletons of the products offer handles for further derivatization. To illustrate this point, the product **3a** was treated with hydrazine and ethylenediamine to give the phtalazinone **4** and imidazoisoindole **5** in excellent yields,[13] respectively, which exhibit antiviral and antibacterial activities. Futhermore, product **3a** could also be easily transformed to the corresponding isoindolin-1-one **6** through a amine substitution reaction (Scheme 2B).[14] The versatilities and the rapidly preparation of these products revealed that our strategy are highly useful and attractive in the synthetic and medicinal chemistry.

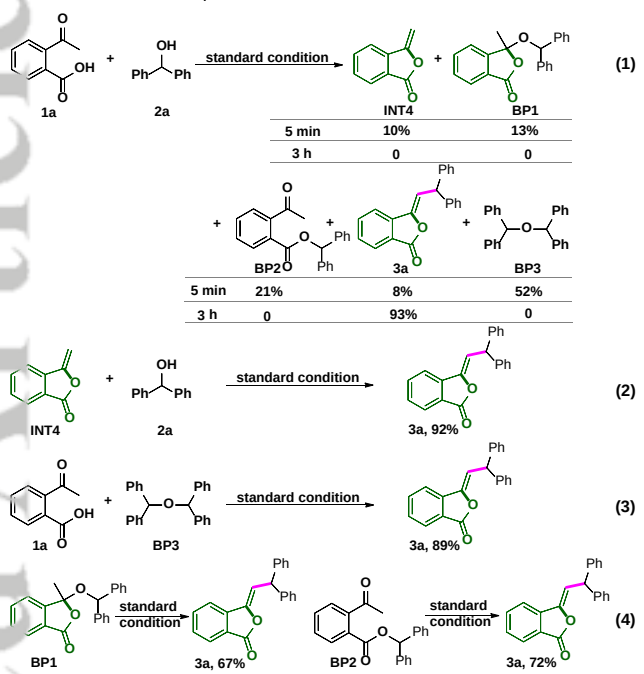
Scheme 2 Gram-scale reactions and derivatization reactions



In order to have a deeper understanding on this transformation and to get further insight into the mechanism, several control experiments were conducted (Scheme 3). When the model reaction was stopped at 5 min, ca. 10% compound **INT4**, 13% compound **BP1**, 21% compound **BP2**, 52% compound **BP3** and 8% **3a** were detected by GC-MS. Upon further heating the reaction mixture for 3 h, **INT4**, **BP1**, **BP2**, and **BP3** disappeared, whereas the yield of **3a** was increased to 93% (Eq. (1) see Supporting Information Figure S1 for more GC-MS details). Pure **INT4** and **BP3** were synthesized following the established procedure. Under the standard reaction conditions, both **INT4** and **BP3** could be converted to **3a** in 92% and 89% yields, respectively (Eq. (2) and (3)).

These results further proved that **INT4** and **BP3** would be the key intermediates in this reaction. Furthermore, isolated compound **BP1** and **BP2** were proven to reformed the substrates **1a** and **2a** and further converted to **3a** under the standard reaction conditions, respectively (Eq. (4) see Supporting Information Figures S2 and S3 for more GC-MS details). The results indicated that the compounds **BP1** and **BP2** were the by-products and reformed the substrates through the reversible reactions.

Scheme 3 Control experiments



To better understand the mechanism of this reaction, a density functional theory (DFT) calculation was employed in the same experimental conditions (solvent of chlorobenzene, temperature at 353.15 K, and pressure at 1.00 atm) using M06-2X functional. For one of the reactants, its keto form (**1a**) is more stable, as transformation from keto form to enol form (**1a'**) is an endergonic process by 13.1 kcal mol^{-1}, which goes through transition state (TS) with a large activation free energy of 67.1 kcal mol^{-1} (Figure 1). Therefore, the reaction is more likely to occur between reactants **1a** and **2a**, which is theoretically investigated here. In this reaction, POMs provide an acidic environment similar to protonic acid, thus, a simple H_3O^+-H_2O model was used to estimate the Gibbs free energy changes during protonation and deprotonation processes. There are three potential sites for protonation of reactant **1a**, including carbonyl oxygen atom in ketone group (O1), carbonyl (O2) and hydroxyl (O3) oxygen atoms in acid group. Theoretical calculation results (Figure S4) show that regardless of the conformation of reactant **1a**, O1 atom is the most potential protonation site, followed by O2 atom. Additionally, the protonation process on O3 atom is endergonic by 13.8-19.4 kcal mol^{-1}, which is unlikely to occur. Different from reactant **1a**, reactant **2a** has only one potential protonation site. Initially, reactants **1a** and **2a** are readily protonated to form **INT1** and **INT5**, which are exergonic processes by 7.3 and 2.6 kcal mol^{-1}, respectively.

It was observed experimentally that the detected **INT4** can replace reactant **1a** reacting with reactant **2a** to form the final product **3a** and **INT4** is able to be directly formed from reactant **1a**. Thus, the formation reaction of **INT4** from reactant **1a** is firstly calculated in details (Figure 1A). After protonation process of reactant **1a**, the produced **INT1** undergoes intramolecular cyclization reaction through **TS1** with an activation free energy of 29.2 kcal mol^{-1} to form cyclic intermediate **INT2**. In this cyclization process, nucleophilic attack of O3 atom and proton transfer from O3 atom to O1 atom proceed in an asynchronous-concerted fashion. The subsequent dehydration process of **INT2** readily proceeds thought **TS2** to form **INT3**, which is nearly barrierless. After deprotonation process of **INT3**, the experimental detected **INT4** is formed from reactant **1a**, which is an endergonic process by 4.8 kcal mol^{-1}. Furthermore, another two pathways separately induced by protonation on O1 and O2 atoms of reactant **1a**, which also undergo intramolecular cyclization reaction, dehydration and deprotonation processes successively, could be ruled out because of much higher activation free energies (Figure S5). Next, the reaction between reactant **2a** and **INT4** to form the final product **3a** is theoretically studied (Figure 1B). After protonation process of reactant **2a**, the generated **INT5** immediately occurs dehydration process via **TS3** with a small activation free energy of 2.5 kcal mol^{-1} to form a more stable carbocation intermediate **INT6**. Then, **INT6** reacts with **INT4** through **TS4** with an activation free energy of 12.8 kcal mol^{-1} to form **INT7**. Finally, deprotonation process of **INT7** leads to the final product **3a**. The whole reaction producing **3a** from **2a** is an exergonic process by 5.9 kcal mol^{-1}.

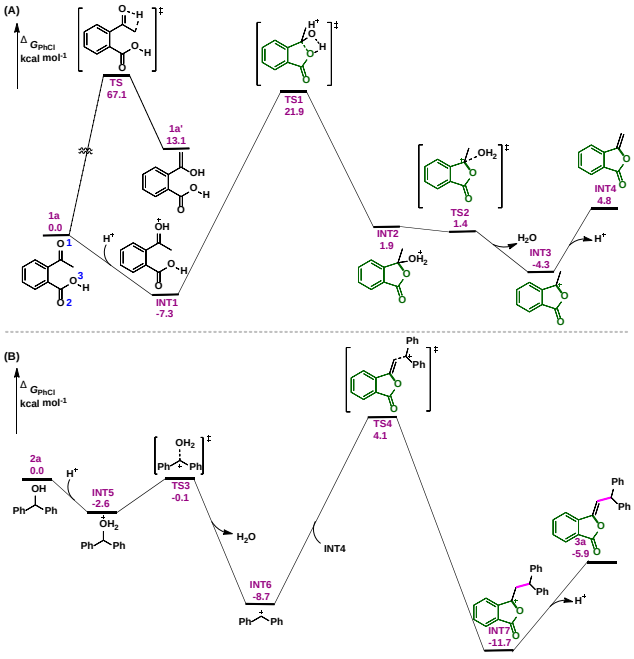


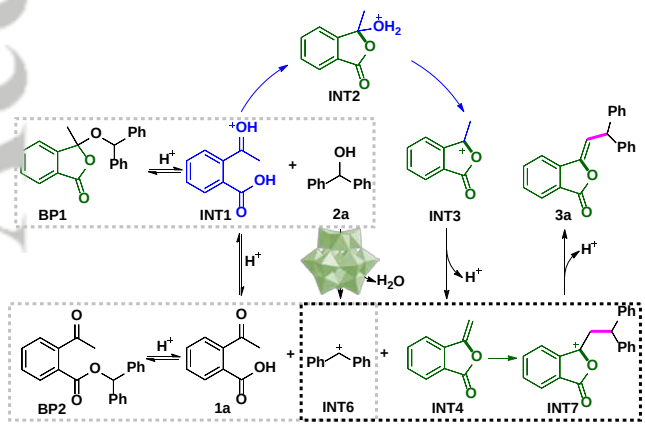
Figure 1 Proposed reaction mechanism and predicted relative Gibbs free energies based on DFT calculation. (A) the formation reaction of **INT4** from reactant **1a**; (B) the reaction forming the final product **3a**.

In the experiment, two major by-products **BP2** and **BP3** are observed in the earlier stage of reaction and final product **3a** is formed with high yield in the later stage of reaction. To explain the experimental observations, theoretical calculations of two side reactions forming major by-products **BP2** and **BP3** are performed (Figure S6). **INT6** from **2a** reacting with **INT4** and reactants **1a-1** and **2a** to respectively form final product **3a** and by-products **BP2** and **BP3** are three competitive reactions. As discussed above, the formation of **INT4** needs to overcome a high activation free energy of 29.2 kcal mol^{-1}. What's more, the activation free energy (12.8 kcal mol^{-1}) of **INT6** reacting with **INT4** to form final product **3a** is higher than those (4.6 and 8.0 kcal mol^{-1}) of two side reactions forming by-products **BP2** and **BP3**. Therefore, two side reactions forming by-products **BP2** and **BP3** are dominant reactions in the earlier stage of reaction. These two side reactions are reversible reactions, as free energy changes are nearly unchanged from **2a** to **BP2** (0.4 kcal mol^{-1}) and **BP3** (-0.5 kcal mol^{-1}). The reaction forming

final product **3a** is exergonic reaction, as free energy change from **2a** to **3a** is -5.9 kcal mol^{-1}. Therefore, reaction forming final product **3a** is dominant reaction in the later stage of reaction. A summary of proposed reaction mechanism and calculated free energies can be seen in Figure S7. Furthermore, to explain the *Z*-selectivity of the products, we have also calculated the Gibbs free energies of *Z* and *E* configurations of product **3a**, which shows the Gibbs free energy of *Z*-configuration is 1.7 kcal mol^{-1} smaller than that of E-configuration. That is to say, *Z*-configuration of product is more stable than its *E*-configuration. Thus, energy stability is one driven force to obtain *Z*-configuration of product. Besides the aspect of Gibbs free energy, we can also analyze from the aspect of geometry. According to our reaction mechanism, **INT6** electrophilic attacks **INT4** with planar structure from vertical direction to form **INT7**. Observing the geometry of **INT7** (Figure S8), dihedral angle ∠C1-C8-C9-C10 is larger than 90° while dihedral angle ∠O1-C8-C9-C10 is smaller than 90°, which shows that it tends to form product **3a** with Z-configuration after deprotonation process. Comparing the geometries of *Z* and *E* configurations (Figure S9), the marked bond angles in *Z*-configuration are smaller than the corresponding ones in *E*-configuration while the marked bond distance in *Z*-configuration is larger than that in *E*-configuration, which shows that *Z*-configuration should have smaller steric resistance than *E*-configuration. Thus, steric hindrance effect is another driven force to obtain *Z*-configuration of products. All calculated results are in good agreement with the experimental observations.

Based on the above results and related literature studies, a plausible mechanism is proposed in Scheme 4. It is believed that the acid catalyst initially protonates the **1a** to provide **INT1**, which has a better nucleophilic site than **1a**, thus enabling the subsequent nucleophilic attack of carboxyl to afford **INT2**. Alternatively, **INT1** could also experience nucleophilic attack of **2a** followed by deprotonation and dehydration to form by-product **BP1**. The undesired by-product **BP1** could reform **INT1** and **2a** through the reversible reactions. After dehydration of **INT2**, the carbocation species **INT3** were generated, followed by the deprotonation to form **INT4**. Meanwhile, under the promotion of heteropoly acid $H_3PMo_{12}O_{40}$, carbocation species **INT6** would be generated directly by protonation/dehydration of the alcohol **2a**. Subsequently, **INT6** electrophilic attack on **INT4** to afford the carbocation species **INT7**, which produce desired product **3a** through the deprotonation process. **INT6** could also electrophilic attack on carboxyl of **1a** leads to the formation of the corresponding ester **BP2**, which would reform **INT6** and **1a** under the acidic condition.

Scheme 4 Proposed mechanism



Conclusions

In summary, we have developed a tandem C–O and C–C bond formation via environmentally benign catalyst $H_3PMo_{12}O_{40}$-catalyzed cyclization and coupling reaction to regio- and stereoselective synthesis the (*Z*)-3-ylidenephthalides in good to excellent yields, which also opens a new reaction space for the selective coupling of carbonyls or carboxyl with alcohols. Overall, the reaction features an eco-friendly reaction conditions, highly atom efficient, facile scalability, and easy derivatization of the products to drugs and bioactive compounds. Detailed mechanistic studies and DFT calculations reveal that the reaction involves the well-known esterification and cyclization reactions, the corresponding by-product would reform the substrates to generate the desired product due to their different stability in the acidic reaction conditions.

Experimental

Gneral procedure for the synthesis of products 3: In a reaction vial of 4 mL, 2-acetylbenzoic acid (**1**, 0.3 mmol), diphenylmethanol (**2**, 0.2 mmol), $H_3PMo_{12}O_{40}$ (1.5 mol%) and PhCl (1 mL) were added. Then the reaction was carried out in screw cap vials with a Teflon seal at 80 °C for 3 h. After cooling to room temperature, the mixture was further purified by column chromatography (petroleum ether/EtOAc) to afford the desired products.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

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References

[1] (a) Rukachaisirikul, V.; Rodglin, A.; Sukpondma, Y.; Phongpaichit, S.; Batong J.; Sakayaroj, J. Phthalide and Isocoumarin Derivatives Produced by an Acremonium sp. Isolated from a Mangrove Rhizophora Apiculata. *J. Nat. Pro*. **2012**, *75*, 853–858; (b) Ortar, G.; Moriello, A. S.; Morera, E.; Nalli, M.; Di Marzo. V.; De Petrocellis L. 3-Ylidenephthalides as a New Class of Transient Receptor Potential Channel TRPA1 and TRPM8 Modulators. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 5614–5618; (c) Yang, H.; Hu, G.; Chen, J.; Wang, Y.; Wang, H. Synthesis, Resolution, and Antiplatelet Activity of 3-Substituted 1(3H)-Isobenzofuranone. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 5210–5213; (d) Ge, Y.; Han, Z.; Wang, Z.; Feng, C.; Zhao, Q.; Lin G.; Ding, K. Ir-SpinPHOX Catalyzed Enantioselective Hydrogenation of 3-Ylidenephthalides. *Angew. Chem. Int. Ed*. **2018**, *57*, 13140–13144; (e) Quéméner, A. S.; Maillasson, M.; Arzel, L.; Sicard, B.; Vomiandry, R.; Mortier, E.; Dubreuil, D.; Jacques, Y.; Lebreton J.; Mathé-Allainmat, M. Discovery of a Small-molecule Inhibitor of Interleukin 15: Pharmacophore-based Virtual Screening and Hit Optimization. *J. Med. Chem*. **2017**, *60*, 6249–6272.

[2] (a) Lee, K. Y.; Kim J. M.; Kim, J. N. Facile Synthesis of 3-Alkylidene-3H-isobenzofuranones from the Baylis-Hillman Reaction of 2-Carboxybenzaldehyde. *Synlett*. **2003**, *2003*, 0357–0360; (b) Shapiro, S. L.; Geiger K.; Freedman, L. Indandione Anticoagulants. *J. Org. Chem*. **1960**, *25*, 1860–1865; (c) Zhu, T.; Mou, C.; Li, B.; Smetankova, M.; Song B.; Chi, Y. N-heterocyclic Carbene-catalyzed δ-Carbon LUMO Activation of Unsaturated Aldehydes. *J. Am. Chem. Soc*. **2015**, *137*, 5658–5661.

[3] (a) Gabriel, S.; Michael, A. Ueber die Einwirkung von wasserentziehenden Mitteln auf Säureanhydride. *Ber. Dtsch. Chem. Ges*. **1877**, *10*, 2199–2210; (b) Chopard, P.; Hudson, R.; Searle, R. The Reaction of Stable Phosphoranes with Phthalic Anhydride Case of Cis-trans Isomerism. *Tetrahedron Lett*. **1965**, *6*, 2357–2360; (c) Dussart, N.; Trinh, H. V.; Gueyrard, D. Modified Julia Olefination on Anhydrides: Extension and Limitations. Application to the Synthesis of Maculalactone B. *Org. Lett*. **2016**, *18*, 4790–4793; (d) Safari, Naeimi, J. H.; Khakpour, A. A.; Jondani, R. S.; Khalili, S. D. A Rapid and Efficient Method for Synthesis of New 3-Arylideneisobenzofuran-1(3H)-one Derivatives Catalyzed by Acetic Anhydride under Solvent-free and Microwave Conditions. *J. Mol. Cat. A Chem*. **2007**, *270*, 236–240.

[4] (a) Cámpora, J.; Maya, C. M.; Palma, P.; Carmona, E.; Gutiérrez-Puebla. E.; Ruiz, C. Synthesis and Aldol Reactivity of O−and C−Enolate Complexes of Nickel. *J. Am. Chem. Soc*. **2003**, *125*, 1482–1483; (b) Zhang, M.; Zhang, H.; Han, T.; Ruan, W.; Wen, T. Rh (III)-Catalyzed Oxidative Coupling of Benzoic Acids with Geminal-Substituted Vinyl Acetates: Synthesis of 3-Substituted Isocoumarins. *J. Org. Chem*. **2015**, *80*, 620–627; (c) Nandi, D.; Ghosh, D.; Chen, S. J. B.; Kuo, C.; Wang, N. M.; Lee, H. M. One-Step Synthesis of Isocoumarins and 3-Benzylidenephthalides via Ligandless Pd-Catalyzed Oxidative Coupling of Benzoic Acids and Vinylarenes. *J. Org. Chem*. **2013**, *78*, 3445–3451; (d) Zhao, D.; Lied, F.; Glorius, F. Rh (III)-catalyzed C−H Functionalization/aromatization Cascade with 1, 3-Dienes: a Redox-neutral and Regioselective Access to Isoquinolines. *Chem. Sci*. **2014**, *5*, 2869–2873; (e) Chaudhary, S.; Shyamlal, B. R. K.; Yadav, L.; Tiwari, M. K.; Kumar, K. Ag_2O Nanoparticle-catalyzed Substrate-controlled Regioselectivities: Direct Access to 3-Ylidenephthalides and Isocoumarins. *RSC Adv*. **2018**, *8*, 23152–23162; (f) Jambu, S.; Tamizmani, M.; Jeganmohan, M. Ruthenium (II)-Catalyzed Cyclization of Aromatic Acids with Allylic Acetates via Redox-Free Two-Fold Aromatic/Allylic C−H Activations: Combined Experimental and DFT Studies. *Org. Lett*. **2018**, *20*, 1982–1986; (g) Han, W.; Pu, F.; Fan, J.; Liu, Z.; Shi, X. Rhodium (III)-Catalyzed Tandem C−H Olefination and Oxidative Cyclization of Aromatic Acids with Acrylates for the Synthesis of (*E*)-3-Ylidenephthalides. *Adv. Synth. Catal*. **2017**, *359*, 3520–3525; (h) Liu, Y.; Yang, Y.; Shi, Y.; Wang, X.; Zhang, L.; Cheng, Y.; You, J. Rhodium-Catalyzed Oxidative Coupling of Benzoic Acids with Terminal Alkynes: An Efficient Access to 3-Ylidenephthalides. *Organometallics*. **2016**, *35*, 1350–1353.

[5] (a) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. Regiocontrolled Intramolecular Cyclizations of Carboxylic Acids to Carbon−Carbon Triple Bonds Promoted by Acid or Base Catalyst. *Org. Lett*. **2006**, *8*, 5517–5520; (b) Novák, P.; Correa, A.; Gallardo-Donaire, J.; Martin, R. Synergistic Palladium-Catalyzed $C(sp^3)$−H Activation/$C(sp^3)$−O Bond Formation: A Direct, Step-Economical Route to Benzolactones. *Angew. Chem. Int. Ed*. **2011**, *50*, 12236–12239; (c) Park, J. H.; Bhilare, S. V.; Youn, S. W. NHC-catalyzed Oxidative Cyclization Reactions of 2-Alkynylbenzaldehydes under Aerobic Conditions: Synthesis of O-heterocycles. *Org. Lett*. **2011**, *13*, 2228–2231.

[6] Danoun, G.; Mamone, P.; Gooßen, L. J. One-Pot Synthesis of 3-Alkylidenephthalides from Benzoic Acids by a Rhodium-Catalyzed ortho-C−H Acylation Process. *Chem. Eur. J*. **2013**, *19*, 17287–17290.

[7] (a) Hori, K.; Takaishi, N. A Convenient Synthesis of 3-Phenacylidenephthalides. *Bull. Chem. Soc. Jpn*.,**1988**, *61*, 1791–1792; (b) He, X.; Xue, F. Transition-metal-free Synthesis of (*Z*)-3-Ylidenephthalides from 2-Acyl-benzoic Acids. *Tetrahedron Lett*. **2014**, *55*, 1956–1958; (c) Wang, X. Li, G.; Zhang, X.; Feng, Z.; Jiang, J.; Yang, Y.; Zhang, P. Stereoselective Synthesis of (*Z*)-3-Ylidenephthalides via $AlCl_3$-Mediated Cyclization with 2-Acylbenzoic acids. *Tetrahedron Lett*. **2020**, *61*, 151734.

[8] (a) El-Harairy, A.; Lai, B.; Vaccaro, L.; Li, M.; Gu, Y. A Sulfone-Containing Imidazolium-Based Brønsted Acid Ionic Liquid Catalyst Enables Replacing Dipolar Aprotic Solvents with Butyl Acetate. *Adv. Synth. Catal*. **2019**, *361*, 3342–3350; (b) Lu, B.; Xie, Z.; Lu, J.; Liu, J.; Cui, S.; Ma, Y. Hu, X.; Liu, Y.; Zhong, K. Highly Atom-Economic, Catalyst-Free, and Solvent-Free Synthesis of Phthalazinones. *ACS Sustain. Chem. Eng*. **2018**, *7*, 134–138; (c) Liu, Y.; Majhi, P. K.; Song, R.; Mou, C.; Hao, L.; Chai, H.; Jin Z.; Chi, Y. Carbene-Catalyzed Dynamic Kinetic Resolution and Asymmetric Acylation of Hydroxyphthalides and Related Natural Products. *Angew. Chem. Int. Ed*. **2020**, *59*, 3859–3863; (d) Xie, C.; Song, J.; Wu, H.; Hu, Y.; Liu, H.; Zhang, Z.; Zhang, P.; Chen, B.; Han, B. Ambient Reductive Amination of Levulinic Acid to Pyrrolidones over Pt Nanocatalysts on Porous TiO_2 Nanosheets. *J. Am. Chem. Soc*. **2019**, *141*, 4002–4009.

[9] (a) Morgan, D. O.; Ollis W. D.; Stanforth, S. P. Preparation and Cycloaddition Reactions of Novel Heterocyclic Mesomeric Betaines. *Tetrahedron*. **2000**, *56*, 5523–5534; (b) Li, G.; Yin, D.; Liang, X. A Facile Synthesis of 3-Substituted Phthalides. *Synth. Commun*. **2004**, *34*, 1183–1189.

[10] (a) Yang, G.; Liu, Y.; Li, K.; Liu, W.; Yu, B.; Hu, C. $H_3PMo_{12}O_{40}$-Catalyzed Coupling of Diarylmethanols with Epoxides/diols/aldehydes toward Polyaryl-substituted Aldehydes. *Chin. Chem. Lett*. **2020**, *31*, 3233–3236; (b) Yang, G.; Wu, X.; Yu, B.; Hu, C. Ionic Liquid from Vitamin B1 Analogue and Heteropolyacid: A Recyclable Heterogeneous Catalyst for Dehydrative Coupling in Organic Carbonate. *ACS Sustain. Chem. Eng*. **2019**, *7*, 3727–3732; (c) Yang, G.; Shang, S.; Yu, B.; Hu, C. Ce (III)-Containing Tungstotellurate (VI) with a Sandwich Structure: an Efficient Lewis Acid-base Catalyst for the Condensation Cyclization of 1, 3-Diketones with Hydrazines/hydrazides or Diamines. *Inorg. Chem. Front*. **2018**, *5*, 2472–2477.

[11] Yang, G.; Zhang, N.; Ma, N.; Yu, B.; Hu, C. An Atom-Economical Route to Substituted β-Arylethyl Ketones: Phosphomolybdic Acid-Catalyzed Carbohydroxylation of Terminal Alkynes in Organic Carbonate. *Adv. Synth. Catal*. **2017**, *359*, 926–932.

[12] CCDC 2047476, 2047477 and 2047476 (**3a**, **3i** and **3q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[13] (a) Ibrahim, H. S.; Eldehna, W. M.; Abdel-Aziz, H. A.; Elaasser, M. M.; Abdel-Aziz, M. M. Improvement of Antibacterial Activity of Some Sulfa Drugs Through Linkage to Certain Phthalazin-1(2H)-one Scaffolds. *Eur. J. Med. Chem*. **2014**, *85*, 480–486; (b) Zamilpa, A.; Herrera-Ruiz, M.; Del Olmo, E.; López-Pérez, J. L.; Tortoriello, J.; San Feliciano, A. [1, 3] Diazaheterofused Isoindolol Derivatives Displaying Anxiolytic-like Effects on Mice. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4016–4021.

[14] Irudayanathan, F. M.; Noh, J.; Choi, J.; Lee, S. Copper-Catalyzed Selective Synthesis of Isoindolin-1-Ones and Isoquinolin-1-Ones from The Three-Component Coupling of 2-Halobenzoic Acid, Alkynylcarboxylic Acid and Ammonium Acetate. *Adv. Synth. Catal*. **2014**, *356*, 3433–3442.

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Entry for the Table of Contents

Regio- and Stereoselective Synthesis of (*Z*)-3-Ylidenephthalides via $H_3PMo_{12}O_{40}$-Catalyzed Cyclization of 2-Acylbenzoic Acids with Benzylic Alcohols

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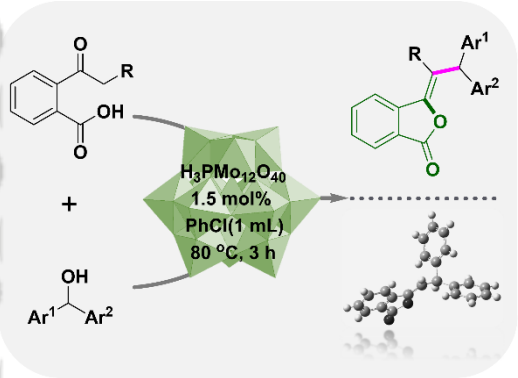

+ *A new reaction site and good site-selectivity*
+ *Regio- and Stereo- selective synthesize*
+ *Benign reaction conditions and atom efficient*
+ *GC-MS characteristics and DFT calculations*
+ *Derivatization of the drugs and bioactive compounds*

A regio- and stereoselective synthesis of (*Z*)-3-ylidenephthalides via $H_3PMo_{12}O_{40}$-catalyzed cyclization of 2-acylbenzoic acids with benzylic alcohols was developed.

