JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

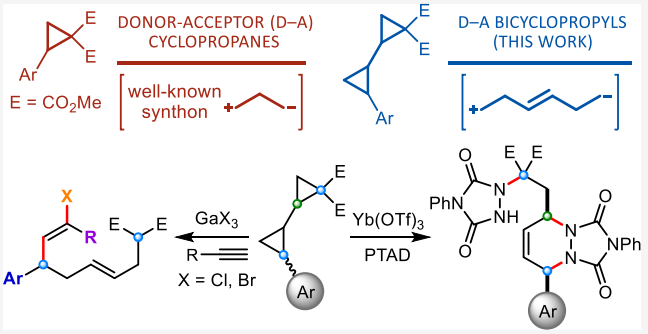
Donor–Acceptor Bicyclopropyls as 1,6-Zwitterionic Intermediates: Synthesis and Reactions with 4-Phenyl-1,2,4-triazoline-3,5-dione and Terminal Acetylenes

Konstantin V. Potapov,[†] Dmitry A. Denisov,[†] Valeriia V. Glushkova, Roman A. Novikov,*[,†] and Yury V. Tomilov*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c02293 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The bicyclopropyl system activated by incorporation of donor and acceptor groups in the presence of Lewis acids was used as a synthetic equivalent of 1,6-zwitterions. Opening of both cyclopropane rings in 2′-aryl-1,1′-bicyclopropyl-2,2-dicarboxylates (D–A bicyclopropyl, ABCDs) in the presence of GaI_3 + $Bu_4N^+GaI_4^-$ results in 5-iodo-5-arylpent-2-enylmalonates as products of HI formal 1,6-addition to the bicyclopropyl system. The use of $GaCl_3$ or $GaBr_3$ as a Lewis acid and terminal aryl or alkyl acetylenes as 1,6-zwitterion interceptors allows the alkyl substituent to be grown to give the corresponding acyclic 7-chloro(bromo)-hepta-2,6-dienylmalonates. The reaction of ABCDs with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) catalyzed by $Yb(OTf)_3$ also results in the opening of both cyclopropane rings. The reaction products are tetrahydropyridazine derivatives — (7,9-dioxo-1,6,8-triazabicyclo[4.3.0]non-3-en-2-ylmethyl)malonates — containing one more PTAD moiety in the malonyl group.



INTRODUCTION

Donor–acceptor cyclopropanes (DACs)[1,2] are widely used in organic synthesis[3,4] owing to their ability to react as synthetic equivalents of 1,3-zwitterions (Scheme 1A). Recently, reactions of DACs where they exhibit other reactivity types have also been studied intensely.[5−8] The use of 2-vinylcyclopropane-1,1-dicarboxylates allows one to obtain not only 1,3-zwitterionic reactivity products but also conjugated 1,5-addition products[9,10] (Scheme 1B). Recently, using gallium halides as Lewis acids, our team found[11,12] yet another type of DAC reactivity involving a three-membered ring opening followed by a hydride shift to give rather stable 1,2-zwitterionic gallium complexes (Scheme 1C(a)). In addition, isomeric styrylmalonates[13] and alkylidenemalonates[14] can be used as analogues of DACs and 1,2-zwitterionic intermediates.

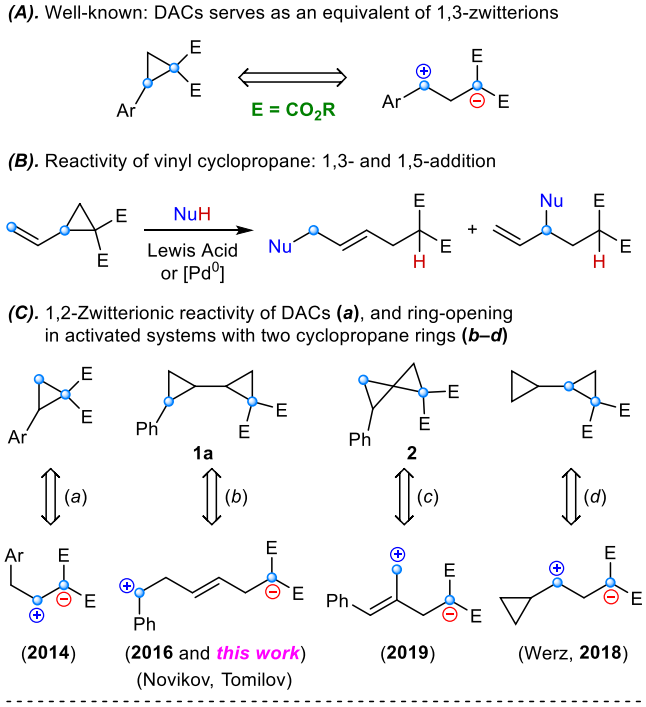
Moreover, systems with a carbocationic center that is remote from the acceptor moiety have almost not been studied. Recently, we began a more detailed study of these systems, in particular, with model substrates containing two cyclopropane moieties in a molecule, such as 2′-phenyl-1,1′-bicyclopropyl-2,2-dicarboxylate (**1a**)[15] (Scheme 1C(b)) and 4-phenylspiropentane-1,1-dicarboxylate (**2**)[16] (Scheme 1C(c)). Using these compounds as examples, it was shown that both cyclopropane rings could be opened in tandem in the presence of various Lewis acids.[15,16] However, only processes of their isomerization to the corresponding dienes and addition of some nucleophiles were mainly studied without variation of substituents. The only known process for **1a** as a formal 1,6-zwitterion is its reaction with $EtAlCl_2$ that leads to formal 1,6-addition of HCl to the bicyclopropyl system (Scheme 1D). Later, Werz showed[17] that only one cyclopropane ring is opened in a bicyclopropyl 1,1-dicarboxylate containing no donor group, which resulted in the classical 1,3-zwitterionic reactivity of such compounds (Scheme 1C(d)).

RESULTS AND DISCUSSION

In this paper, we continued to study the activated bicyclopropyl system that can trap the zwitterions formed *in situ*. To this end, we expanded the range of the starting 2′-aryl-1,1′-bicyclopropyl-2,2-dicarboxylates **1** (ABCDs) (Scheme 1C(b)) using some terminal acetylenes and PTAD (4-phenyl-1,2,4-triazoline-3,5-dione) as unsaturated substrates, as well as by the formal addition of HI *via* the GaI_3/$Bu_4N^+GaI_4^-$ system. We chose both of them as model substrates because of their stability toward Lewis acids, including $GaCl_3$,[18,19] and also because of their high reactivity.

Received: September 25, 2020

Scheme 1. Main Types of D–A Cyclopropane-Based Sources for the Generation of Various Formal 1,*n*-Zwitterionic Synthons



Moreover, the PTAD moiety (in case of its successful coupling with DAC **1**) is of interest in terms of potential biological activity of the resulting compounds that are known for various PTAD derivatives.[20,21] For example, inflachromene, an inhibitor with antineuroinflammatory effects (Figure 1), is one of its famous derivatives.[22]

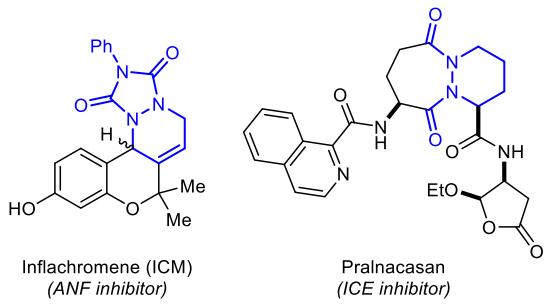
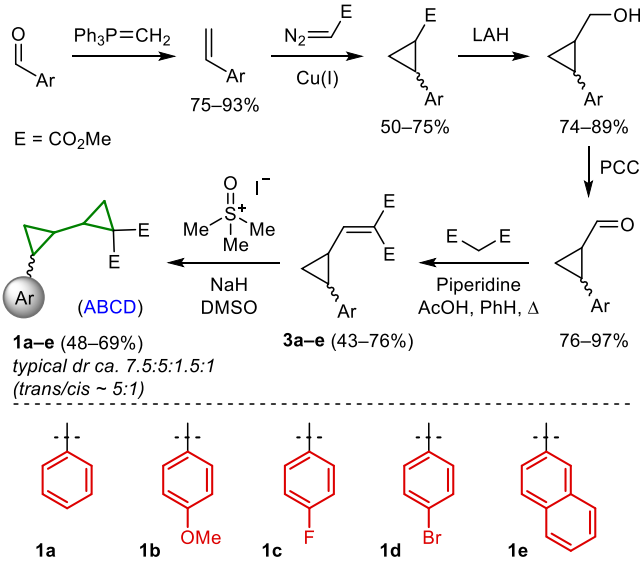


Figure 1. Representative examples of PTAD derivatives and tetra-/hexahydropyridazine skeletons in pharmaceuticals and its analogues.

To obtain substituted 1,1′-bicyclopropyl-2,2-dicarboxylates **1b–e**, we successfully applied the scheme that we developed earlier for synthesizing the simplest phenyl-substituted bicyclopropyl **1a**[15] based on the traditional reaction sequence well proven for D–A cyclopropanes: Knoevenagel condensation and Corey–Chaykovsky cyclopropanation (Scheme 2). At the same time, attempts to use alternative synthetic schemes failed. Therefore, we disregarded the use of the simplest and

Scheme 2. Synthesis of Starting 2′-Aryl-1,1′-bicyclopropyl-2,2-dicarboxylates 1a–e (ABCDs)[a]



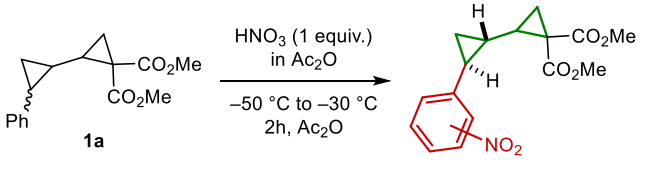
[a]Cu(I) = $Cu(MeCN)_4PF_6$; LAH = $LiAlH_4$; PCC = $PyrH^+CrO_3Cl^-$; E = CO_2Me. See the Experimental Section for detailed information.

most logical method for its preparation by cyclopropanation of the corresponding 2-styrylcyclopropane-1,1-dicarboxylates under any conditions.[15] The double bond in the last compounds proved to be surprisingly nonreactive and did not undergo cyclopropanation, neither under conditions of catalytic or thermal cyclopropanation with diazomethane, nor under Simmons–Smith cyclopropanation conditions. An alternative cyclopropanation approach of 2-vinylcyclopropane-1,1-dicarboxylate using various aryldiazomethanes gives very low yields of the target bicyclopropyls **1**.

The target bicyclopropyls **1a–e** were prepared in six steps from commercially available aromatic aldehydes containing a mixture of four diastereomers (Scheme 2). Previously,[15] the isomeric composition was studied in detail for bicyclopropyl **1a**, and the isomer ratio was estimated to be 6.6:4.7:1.2:1.0. The ratio of trans- and cis-isomers was the same as in the previous vinylcyclopropane **3a** (~5:1). However, we did not pay special attention to it for other substituted ABCDs, because this isomerism should not play a significant role in subsequent reactions that occur with the opening of both cyclopropane rings. As a result, only the E- and Z-isomerism of the resulting double bond is observed.

Nitrophenyl-substituted bicyclopropyl **1f** has also been synthesized (Scheme 3). However, the standard six-step sequence gave very bad yields and a complex mixture and could not be applied. In this case, ABCD **1f** was obtained in a

Scheme 3. Synthesis of 2′-(Nitrophenyl)-1,1′-bicyclopropyl-2,2-dicarboxylate 1f

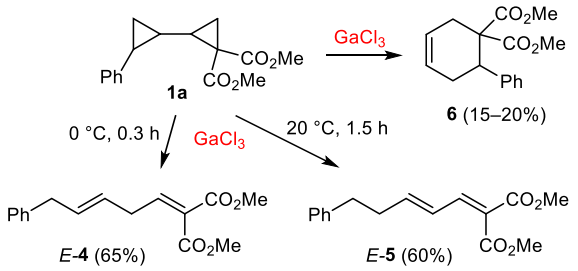


https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX–XXX

high yield by direct nitration of the simple Ph-analogue **1a**. Bicyclopropyl **1f** is formed as a mixture of ortho-/para-isomers with a dominant ortho-isomer. During nitration, the bicyclopropyl system turns out to be unexpectedly stable enough at least at low temperatures.

The previously studied isomerization of bicyclopropyl **1a** in the presence of $GaCl_3$ results in regioisomeric dienes **4** or **5** depending on the reaction conditions, but in each case only in the form of the E-isomer (Scheme 4). The accompanying

Scheme 4. Isomerization of 2′-Phenyl-1,1′-bicyclopropyl-2,2-dicarboxylate 1a in the Presence of $GaCl_3$



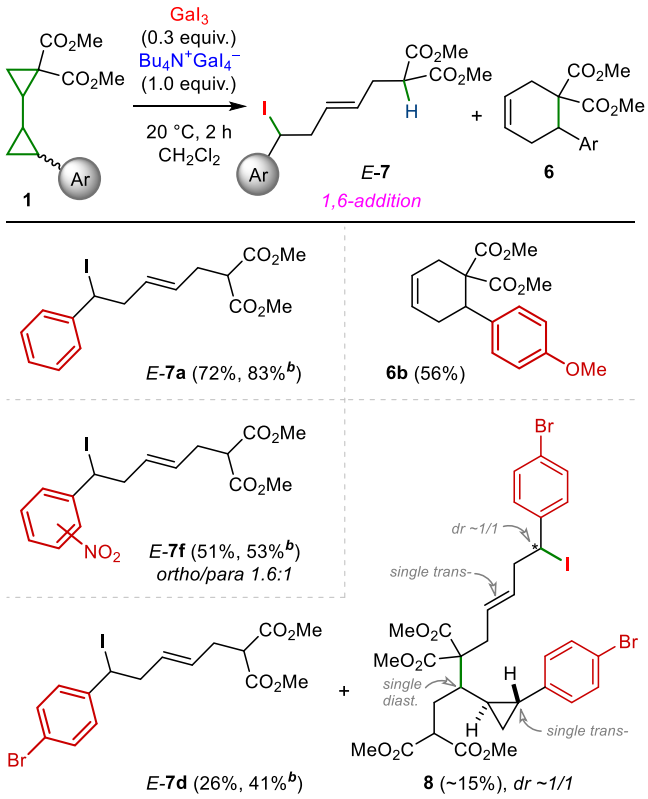
minor process to give cyclohexene **6** occurs through generation of a *Z*-1,6-zwitterionic intermediate or through a sigmatropic rearrangement. The observed ratio of regioisomers **4** (or **5**)/**6** is >3:1.

We showed that approximately the same picture was observed with $GaBr_3$. However, on replacing these Lewis acids with gallium(III) iodide, we found that the predominant reaction pathway changed. In this case, the amount of dienes sharply decreased and 5-iodopent-2-enylmalonate **7** became the main product, while the amount of cyclohexene **6** remained nearly unchanged (Scheme 5; Table 1). The regioselectivity of iodide anion addition as a nucleophile (absence of the 1,3-addition product) and the E-configuration of the C(3)−C(4) double bond in the resulting compound **7** indicate that the *E*-1,6-zwitterion generated upon opening of both cyclopropane rings in ABCD **1a** can be trapped. At the same time, the reason for the change in the reaction pathway in the presence of GaI_3 instead of $GaCl_3$ or $GaBr_3$ lies in a higher nucleophilicity of iodide anions compared to those of chloride and bromide anions (or tetrachlorogallate anions as its transporters[14a]).

Initially, if 1 equiv of gallium iodide was used as the Lewis acid, the yield of iodide **7** was no higher than 40%. We have shown previously in a study of DAC reactions with alkynes in the presence of gallium halides that a halide anion is added not from GaX_3 but from a GaX_4^- anion that is formed upon dismutation of intermediate gallium complexes.[14a] Assuming that the presence of a high GaI_4^- concentration at the initial instant of the reaction can improve the yield of iodide **7**, we decided to optimize the reaction conditions by replacing pure GaI_3 with its mixture with a compound containing the GaI_4^- anion. For this purpose, we used the air-stable tetrabutylammonium salt $Bu_4N^+GaI_4^-$.[23] Indeed, using 0.3 equiv of GaI_3 and 1.0 equiv of $Bu_4N^+GaI_4^-$, we succeeded in increasing the isolated yield of iodide **7** to 83% (Scheme 4; Table 1, entry 4).

Under these conditions, we have studied other bicyclopropyls **1b,d,f** for possibility of the formal 1,6-addition of HI (Scheme 5). In general, bicyclopropyls **1d,f** gave the corresponding products **7f,d** as single E-isomers without problems, however, with lower yields because of the lower stability of iodine derivatives. Methoxy bicyclopropyl **1b** easily

Scheme 5. Formal 1,6-Addition of HI to Bicyclopropyls 1 in the Presence of the $GaI_3/Bu_4N^+GaI_4^-$ System and Scope of the Reaction[a]



[a]Isolated yields. [b]NMR yields.

Table 1. Variation of the Reaction Conditions for the Formal 1,6-Addition of HI to Bicyclopropyl 1a

entry	GaI_3 (equiv)	$Bu_4N^+GaI_4^-$ (equiv)	yield of *E*-7, (%)[a]	yield of **6**, (%)[a]
1	1.0		38	15
2	0.1	1.0	42	~15[b]
3	0.2	1.0	53	~15[b]
4	**0.3**	**1.0**	**83 (72)**[a]	**16**

[a]NMR yields; isolated yields are given in parentheses. [b]Accuracy: ±2−3%.

gives the isomeric cyclohexene **6b** mainly, while the corresponding iodine product could not be isolated.

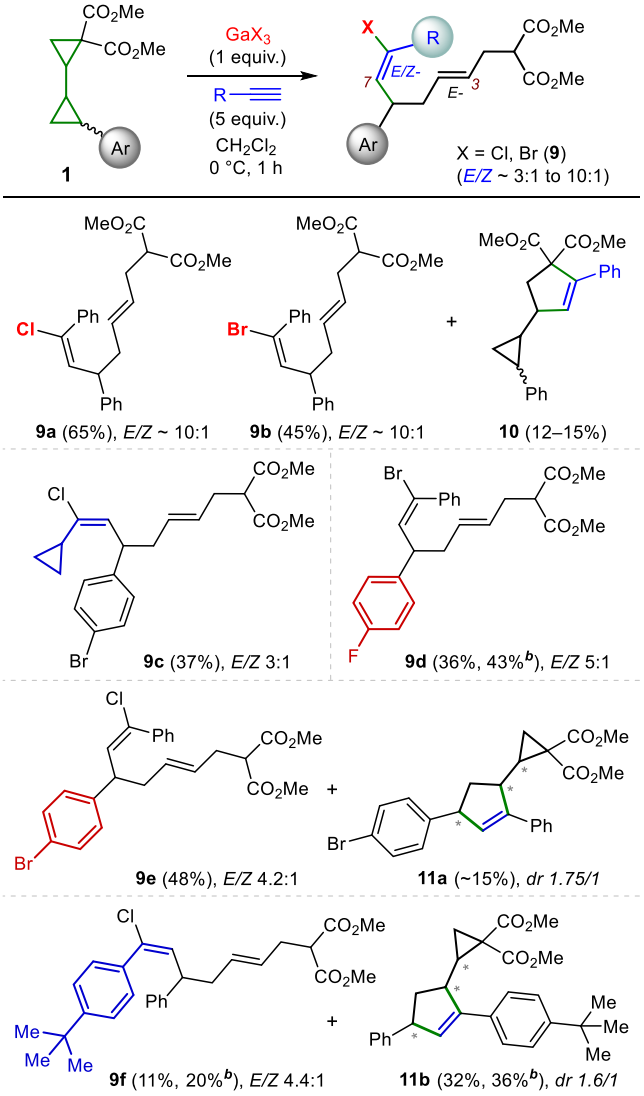
It is also interesting to note selective formation in significant quantities of the dimeric iodine adduct **8** for *para*-Br-substituted bicyclopropyl **1d** (Scheme 5). This compound is assembled from two bicyclopropyl molecules with cleavage of three cyclopropane rings and formal addition of HI, wherein one bicyclopropyl molecule acts as a formal 1,6-zwitterion. Moreover, this "acyclic" iodine product **8** contains four stereocenters, and under the described conditions, it is formed as a mixture of only two detected diastereomers of 16 possible stereoisomers, and with high chemoselectivity to the constructed skeleton. Also, this product can be apparently optimized to higher yields under the deficiency of iodine anions.

Furthermore, we studied the possibility of extending the alkyl chain by the reaction of the 1,6-zwitterion generated from ABCD with phenylacetylene. We previously used this approach

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX

for the efficient addition of terminal acetylenes to 1,2-zwitterions generated from DACs[24] or to substituted methylidenemalonates[14a] in the presence of gallium halides. In this case, the intermediate highly reactive vinyl cations were stabilized by the addition of a halide anion. Indeed, the reaction of bicyclopropyl **1a** with 1 equiv of gallium(III) chloride or bromide in the presence of 4−5 equiv of phenylacetylene gave substituted 2,6-heptadienyl malonates **9a** and **9b** in 65 and 45% yields, respectively (Scheme 6). At

Scheme 6. Three-Component Addition of Acetylenes to ABCDs 1 in the Presence of $GaCl_3$ or $GaBr_3$ and Scope of the Reaction[a]



[a]Isolated yields. [b]NMR yields.

the same time, iodination using GaI_3 is not possible to perform effectively under these reaction conditions and using this halogenation system (similar to Cl and Br). Iodide anions are attached directly to the bicyclopropyl skeleton much more efficiently. Nevertheless, vinyl iodides such as **9** can be formed in low yields, but further substantial developments of iodination process should be performed.

In both cases (Cl and Br), the C(3)−C(4) bond had an E-configuration, while the ratio of E and Z isomers for the C(7)−C(8) bond was ~10:1. The reaction involved the opening of both cyclopropane rings (Figure 2A). Phenylacetylene was

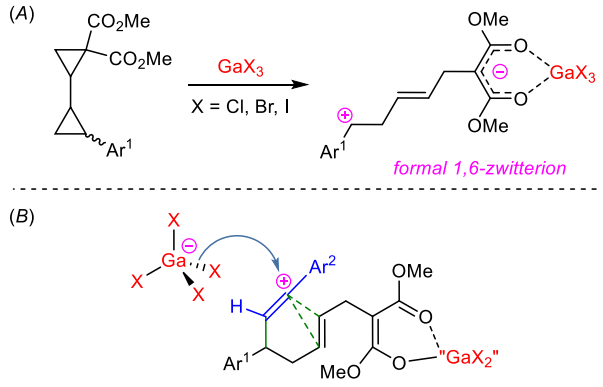


Figure 2. Some main mechanistic features: (A) initial generation of the formal 1,6-zwitterion and (B) a step of trans-selective addition of $GaCl_4^-$ and $GaBr_4^-$ anions to the resulting vinyl cation after phenylacetylene addition.[24]

added regioselectively at the phenyl-substituted C(6) atom. Ultimately, a halovinyl moiety was incorporated into the molecule of the starting substrate **1a**. In addition to the formation of halides **9**, we also detected the formation of cyclopropylcyclopentene **10,** a side product of the formal (3 + 2)-cycloaddition of phenylacetylene to the D−A cyclopropane ring. This may imply that the consecutive opening of small cycles in the 1,1′-bicyclopropyl ABCD system occurred.

The predominant formation of the *E*-C(7)−C(8) double bond can be explained by a partial approach of the cationic center in the intermediate vinyl cation to the C(3)−C(4) double bond and its stabilization, which results in the shielding of one of the sides for attack by the nucleophile (Figure 2B).

Furthermore, we have evaluated some different bicyclopropyls **1** and terminal acetylenes in this three-component process using both $GaCl_3$ and $GaBr_3$ (Scheme 6). Apparently, this process is general in nature. However, it is quite difficult to study for each substrate. The reason lies in the complex structures of products and multiple high reactivity of bicyclopropyls in studied systems. The isolation of pure compounds is also quite laborious in some cases due to its partial decomposition during chromatography. Nevertheless, this is compensated in full by interesting and unknown chemistry of D−A bicyclopropyls and the complex nature of constructed skeletons with multiple functional groups in one synthetic step. Vinyl halide products such as **9** seem to be interesting for further modification by cross-coupling reactions in combination with the use of functional groups.[14a,24]

Therefore, we have successfully obtained the acyclic vinyl halides **9a−f** for bicyclopropyls **1a,c,d** as starting compounds. Phenylacetylene, *para-tert*-butyl phenylacetylene, and aliphatic cyclopropylacetylene have been used as terminal acetylene substrates (Scheme 6). The acyclic vinyl halides **9** were prepared predominantly as 3*E*,7*E*-isomers with 7*E*/7*Z* ratios from 3/1 to 10/1 depending on substituents. This ratio and product yields are lower for more substituted compounds **9c−f**, apparently because of its higher reactivity and not fully optimized reaction conditions.

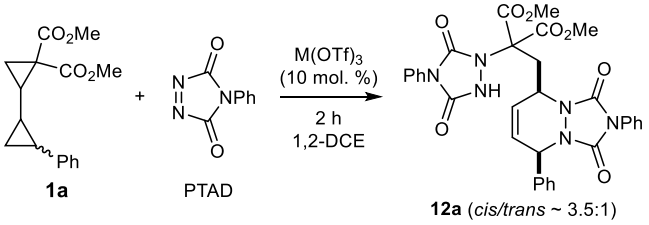
In addition to the formation of vinyl chlorides **9e,f**, we also detected the formation of cyclopropyl cyclopentenes **11a,b** as side products of another formal (3 + 2)-cycloaddition process

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX

(Scheme 6). This type of product was detected only in the cases of these combinations of substrates. Moreover, it is similar to the formation of cyclopentene **10**, but unlike the last, this (3 + 2)-cycloaddition unexpectedly occurs at another 2nd cyclopropane ring in ABCDs **1a,d**. Moreover, for bicyclopropyl **1a** and *para-tert*-butyl phenylacetylene, cyclopropylcyclopentene **11b** is the main product of the reaction. All these facts could be explained through the course of the reaction *via* the 1,6-zwitterionic intermediate (Figure 2).

Furthermore, it is important to explore other options for trapping six-carbon synthons generated from ABCD. PTAD, which is often used to solve problems of this kind, was applied as a highly active interceptor.[18,19,25−27] In fact, we performed the reaction of bicyclopropyl **1a** with a 2-fold excess of PTAD under the conditions of soft catalysis with $Yb(OTf)_3$ and actually obtained one main product of their reaction (**12a**). However, an unexpected structure was found that corresponded to the reaction of **1a** with two PTAD molecules, one of which was involved in the formation of a tetrahydropyridazine ring (Table 2; Scheme 7). Thus, one PTAD equivalent formally acted as a dienophile, while the other one was added to the malonyl moiety.

Table 2. Optimization of Conditions for the Reaction of 1a with PTAD[a]



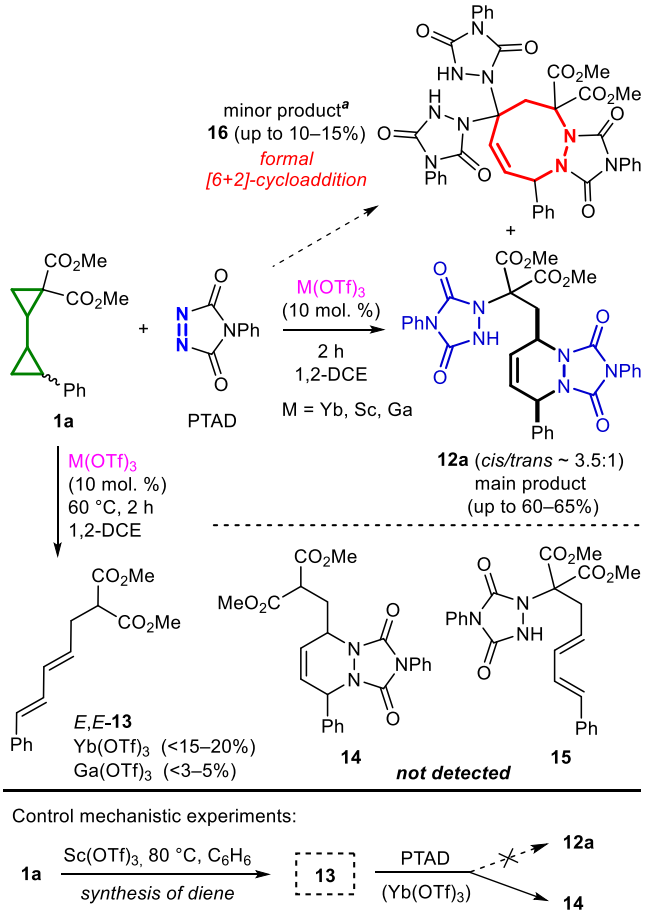
entry	PTAD, equiv	*T*, °C	Lewis acid (10 mol %)	yield of **12a** (%)[b]
1	2.3	20	$Yb(OTf)_3$	5
2	2.3	40	$Yb(OTf)_3$	15
3	2.3	84	$Yb(OTf)_3$	50 (45)[c]
4	2.3	60	$Yb(OTf)_3$	65 (60)[c]
5	2.3	60	$Sc(OTf)_3$	25
6	2.3	60	$Ga(OTf)_3$	38
7	1	60	$Yb(OTf)_3$	22
8	2.3	0−20	$GaCl_3$[d]	0 (c.m.)[e]
9	2.3	0−20	$GaBr_3$[d]	0 (c.m.)[e]

[a]Solvent: DCM for entries 1 and 2; 1,2-DCE for entries 3−7; reaction time = 2 h. [b]NMR yields. [c]Isolated yield, *E*/*Z* ~ 3.5:1. [d]10−100 mol % was used. [e]c.m. = complex mixture.

To optimize the conditions, we studied the effect of various Lewis acids and the effect of temperature on the extent to which this process occurs. Therefore, GaX_3 (X = Cl, Br) is too active and leads to complete polymerization/resinification of the reaction mixture. Therefore, for this reason, it cannot be used for catalysis. As a result of optimization, the reaction using 10 mol % $Yb(OTf)_3$ at a temperature of 60 °C gave compound **12a** in 65% yield (Table 2). It should be noted that under the same conditions, but in the absence of PTAD, bicyclopropyl **1a** is converted to diene **12** by less than 20% yield, that is, the presence of PTAD in the reaction mixture significantly accelerates the opening of the bicyclopropyl system.

The use of Ga(III) triflate also proved to be possible, although by itself and in the absence of PTAD, it does not

Scheme 7. Reaction of ABCD 1a with PTAD[a]



[a]Compound **16** is less stable under reaction conditions and on SiO_2 and decomposes during isolation attempts; it was analyzed directly in the reaction mixtures using the complex $^1H/^{13}C/^{15}N$ NMR approach.

cause the isomerization of bicyclopropyl **1a** to diene **12**. This fact indicates that the preceding carbocationic intermediates rather than the diene are involved in the formation of compound **12a**. Moreover, this is confirmed by additional mechanistic experiments (Scheme 7). It is interesting to note that under optimized conditions using the equimolar **1a**/PTAD ratio, the reaction still gives only the double addition product **12a** but in a lower yield (Table 2, entry 7). In all the cases, no products of addition of 1 equiv of PTAD to **1a** (**14**, **15**) were detected.

Instead, a detailed analysis of reaction mixtures under various conditions revealed that, along with **12a**, an even more exotic compound **16** was formed in 10−15% yield (Scheme 7). Its most notable feature is that an eight-membered heterocycle is formed with participation of as many as three PTAD molecules. Formally, this process corresponds to [6 + 2]-cycloaddition, which is the first example of such a reaction of a bicyclopropyl system with any multiple bonds. The final structure is formed upon addition of two more PTAD molecules by an ene-reaction. However, as the resulting compound **16** is not sufficiently stable, we failed to isolate it in an individual state. Therefore, it was analyzed by NMR directly in the reaction mixtures.

The structures of the resulting compounds **12a** and **16** were analyzed in detail and confirmed using $^1H/^{13}C/^{15}N$ NMR spectroscopy (Figure 3). The configuration of the tetrahy-

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX

dropyridazine ring substituents was determined from the key cross-peaks in the NOESY spectra, which showed their cis arrangement (Figure 3).

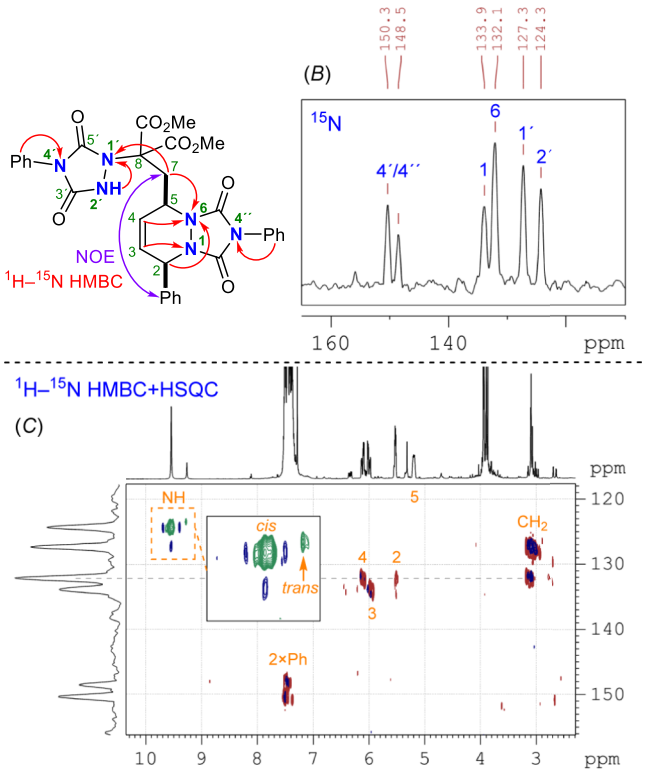


Figure 3. ^{15}N-NMR-based structure determination for the diadduct **12a**: (A) key $^2J/^3J$ ^{1}H–^{15}N interactions and ^{1}H–^{1}H NOE; (B) reconstructed full ^{15}N NMR spectrum with signal assignments; and (C) superimposed 2D ^{1}H–^{15}N HMBC and HSQC NMR spectra.

Analysis of ^{15}N spectra was used as the main method for resolving the structure. They were recorded using inverse ^{1}H–^{15}N HMBC/HSQC 2D methods based on the natural abundance of the ^{15}N isotope. All the signals of nitrogen atoms in the ^{15}N spectrum were totally assigned, and the C/N framework of the molecule was completely analyzed (Figure 3). The structure of compound **16** was determined in a similar way (Figure 4).

In order to expand the scope of the objects of our study, we used the series of 2′-aryl-1,1′-bicyclopropyl-2,2-dicarboxylates (ABCDs) **1b–f** that we obtained. A similar reaction of these compounds with PTAD in the presence of 10 mol % Yb(OTf)$_3$ resulted in a series of new 5,8-dihydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-diones **12b–e** in moderate yields and with even higher cis/trans isomer ratios up to 10:1 (Scheme 8). The best yields were achieved in the case of donor aryl

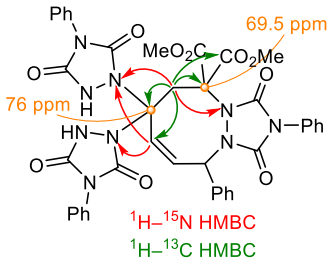
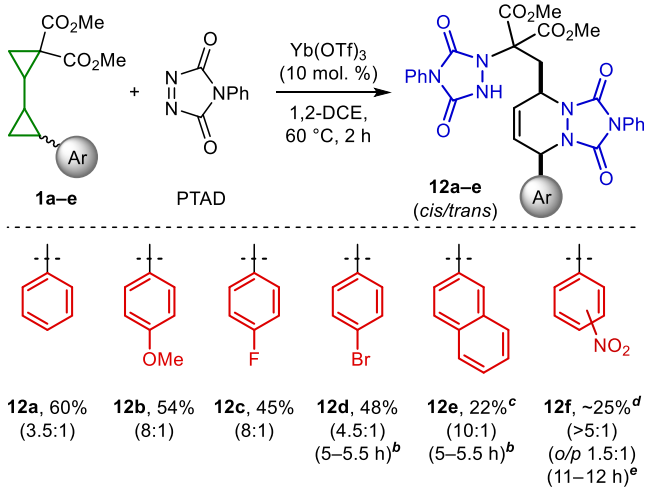


Figure 4. Registered key $^2J/^3J$ ^{1}H–^{13}C and ^{1}H–^{15}N interactions in 2D HMBC NMR spectra for the structure determination of the minor [6 + 2]-triadduct **16**.

Scheme 8. Scope of the Reaction of ABCDs 1a–e with PTAD[a]



[a]Isolated yields; cis/trans ratio is given in parentheses. [b]Reaction time for **12d,e** is 5–5.5 h. [c]Compound **12e** was isolated, but not in a pure form, due to its partial decomposition during the isolation process. [d]NMR yield, compound **12f** was not isolated because of decomposition. [e]Reaction time for **12f** is 11–12 h.

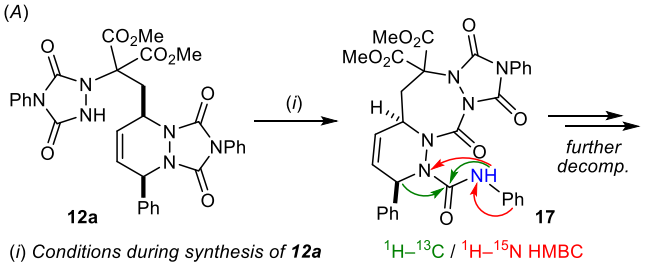
substituents, while the lowest yield of 22% was obtained in the case of the naphthyl substituent. Apparently, in all the cases, the yield decreases significantly due to partial decomposition of the products during the reaction and isolation. For bicyclopropyl **1f**, we were unable to isolate the corresponding nitrogen product **12f** due to its complete decomposition during chromatography by influence of the nitro group. However, it is an important fact that the reaction proceeds for both donor and acceptor substituents in bicyclopropyls **1**.

However, we managed to describe one of the decomposition processes of **12a** in the reaction mixture during its synthesis using complex 2D ^{1}H–^{13}C and ^{1}H–^{15}N NMR techniques applied to several reaction mixtures. One of the decomposition pathways is associated with the cleavage of the triazolidinone fragment and further cyclization involving NH-groups under Lewis acid catalysis. Therefore, compound **17** was detected in the reaction mixtures, which cannot be isolated due to its low stability (Scheme 9A). Also, we have tried to deprotect triazolidinone "protective" groups in the product **12a** under basic conditions, however, with poor success. We could only detect a possible formation of a not very stable hydrazine derivative **18** with low yields in the reaction mixtures without a possibility of its isolation (Scheme 8B).

The assumed reaction mechanism taking the involvement of PTAD in the opening of the bicyclopropyl system into account[25] is apparently related to the opening of the first activated cyclopropane ring. In this case, the formation of the first C–N bond and the subsequent opening of the second cyclopropane ring, followed by the formation of yet another C–N bond occur rather quickly *via* transition states **I–IV** (Scheme 10). Furthermore, cyclization with formation of a pyridazine ring, followed by proton transfer in intermediate **V** occur to give the target product and recover M(OTf)$_3$ for the

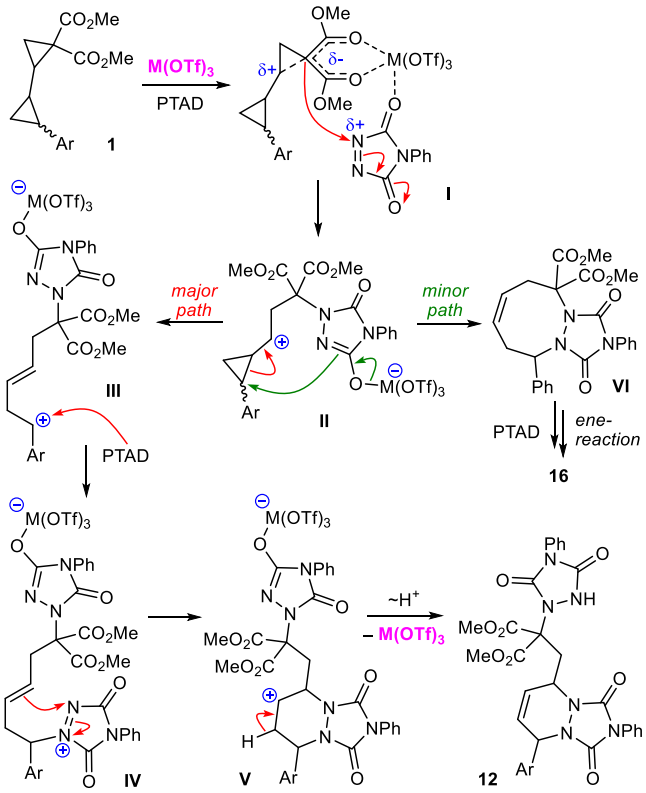
https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 9. (A) One of Further Decomposition Side-Processes in the Reaction Mixture during Synthesis of 12a Detected by Detailed NMR Analysis; (B) Attempts of Deprotection of Compound 12a to Synthesize a Dihydrazine Derivative[a]



[a]Compounds **17** and **18** are less stable under reaction conditions and on SiO_2, and decompose during isolation attempts; they were analyzed directly in the reaction mixtures using complex ^{1}H, ^{13}C, and ^{15}N NMR approaches.

Scheme 10. Proposed Mechanism for the Reaction of ABCD with PTAD



new catalytic cycle. This mechanism is partially confirmed by several additional mechanistic experiments that we performed (Scheme 10), as well as the detected formation of an eight-membered ring in compound **16** as a side product.

CONCLUSIONS

In summary, we have developed a strategy for utilizing activated bicyclopropyl systems as possible sources of 1,6-zwitterionic intermediates. In fact, opening of both cycles in 2′-aryl-1,1′-bicyclopropyl-2,2-dicarboxylates formally corresponds to the 1,6-addition of HI to give 5-iodo-5-arylpent-2-enylmalonates. The use of gallium chloride or bromide in the presence of terminal aryl or alkyl acetylenes allows the alkenyl chain to be extended by incorporating an additional halovinyl moiety to give the corresponding 7-halohepta-2,6-dienyl malonates with the predominant E-configuration of the double bonds. The reaction of 1,1′-bicyclopropyl-2,2-dicarboxylates **1a–f** with PTAD under catalysis of 10 mol % $Yb(OTf)_3$, regardless of the reagent ratio, occurs with the addition of 2 equiv of PTAD, one of which forms the 1,6,8-triazabicyclo[4.3.0]non-3-ene system, while the second one is added to the malonyl moiety.

EXPERIMENTAL SECTION

General Experimental Details. All reagents used were of commercial grade. All operations were carried out under a dry argon atmosphere. TLC analysis was performed on Silufol chromatographic plates. For preparative chromatography, silica gel 60 (0.040–0.063 mm) was used. ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded on 400 MHz (400, 101, and 40 MHz, respectively) and 300 MHz (300, 75, and 30 MHz, respectively) spectrometers in $CDCl_3$ containing 0.05% Me_4Si as the internal standard. Assignments of ^{1}H, ^{13}C, and ^{15}N signals were made with the aid of 2D z-gradient-selected COSY, TOCSY, NOESY, HSQC/edited-HSQC, HMBC/constant-time HMBC, and ^{1}H–^{15}N HSQC/HMBC spectra, if it was necessary.[28] IR spectra were obtained on a FT-IR spectrometer in $CHCl_3$ solution (1%). Mass spectra were recorded using electron impact ionization (70 eV, direct inlet probe). High-resolution mass spectra were obtained using simultaneous electrospray ionization.[29] The elemental compositions were determined on a CHN analyzer instrument.

Synthesis of Starting Substituted Styrenes. Substituted styrenes were synthesized from the corresponding aromatic aldehydes according to the literature procedure.[31] ^{1}H and ^{13}C{^{1}H} spectroscopic data and physical data (bp or mp) are identical to those described in the literature: 1-methoxy-4-vinylbenzene [ref 32], 1-bromo-4-vinylbenzene [ref 32], 1-fluoro-4-vinylbenzene [ref 32], and 2-vinylnaphthalene [ref 32].

Typical Experimental Procedure for the Preparation of Methyl 2-Arylcyclopropane-1-carboxylates. Method A. To the boiling mixture of $Cu(acac)_2$ (1.3 g, 5 mmol) in 25 mL of CH_2Cl_2, methyl diazoacetate (0.92 g, 9 mmol) was added in a single portion, followed by the addition of styrene solution (104 g, 1 mol) in 75 mL of CH_2Cl_2. After that, the remaining solution of methyl diazoacetate (49.1 g, 0.49 mol) in 50 mL of CH_2Cl_2 was added (20 mL/h). The resulting mixture was refluxed for 15 min, cooled to room temperature, passed through a silica gel plug, and evaporated. The crude product was fractionated to obtain the desired methyl-2-phenylcyclopropane-1-carboxylate.

Methyl 2-Phenylcyclopropane-1-carboxylate.[33] Colorless liquid (55.2 g, 52%, bp: 55–57 °C/0.1 Torr, cis/trans ratio = 2:3). ^{1}H and ^{13}C{^{1}H} spectroscopic data are identical to those described in the literature [ref 33].

Typical Experimental Procedure for the Preparation of Methyl 2-Arylcyclopropane-1-carboxylates. Method B. To the stirred mixture of the corresponding styrene (26 mmol) and $Cu(MeCN)_4PF_6$ (490 mg, 1.32 mmol) in 25 mL of CH_2Cl_2 under an argon atmosphere, a solution of methyl diazoacetate (2.64 g, 26 mmol) in 16 mL of CH_2Cl_2 (5 mL/h) was added. The mixture was stirred at room temperature overnight. The resulting solution was passed through a silica gel plug and evaporated. The crude product

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX–XXX

was separated by column chromatography on silica gel (eluent: hexane−AcOEt) to afford the desired compound.

Methyl 2-(4-Methoxyphenyl)cyclopropane-1-carboxylate.[33] Colorless liquid (50%, 3.48 g). ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 33].

Methyl 2-(4-Fluorophenyl)cyclopropane-1-carboxylate.[34] Yield: 55% (2.8 g), colorless liquid, cis/trans = 2:3. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 34].

Methyl 2-(4-Bromophenyl)cyclopropanecarboxylate.[35] Yield: 57% (8.7 g), colorless liquid, cis/trans = 1:2. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 35].

Methyl 2-(Naphthalen-2-yl)cyclopropane-1-carboxylate.[36] Yield: 52% (3.1 g), colorless oil, cis/trans = 1:3.5. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 36].

Typical Experimental Procedure for the Preparation of (2-Arylcyclopropyl)methanols. A solution of 2-phenylcyclopropane-1-carboxylate (6.53 g, 37.1 mmol) in 150 mL of dry Et_2O was added dropwise to the stirred suspension of $LiAlH_4$ (2.11 g, 55.6 mmol) in 250 mL of dry Et_2O. The reaction mixture was refluxed for 2 h, followed by cooling in an ice-bath. Then, 2 mL of H_2O, 2 mL of NaOH (water solution, 15% w/w), and 6 mL of H_2O were added in sequence. The cooling bath was removed and the mixture was stirred for 15 min. The precipitate was filtered and washed with Et_2O. The organic phase was washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed in vacuo to afford the desire product (4.40 g, 80%, cis/trans = 3:4) as a colorless liquid. The obtained product was used without additional purification.

(2-Phenylcyclopropyl)methanol.[37] Yield: 80% (37.7 g), colorless liquid, cis/trans = 3:4. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 37].

(2-(4-Methoxyphenyl)cyclopropyl)methanol.[37] Yield: 87% (5.76 g), light yellow oil, cis/trans = 2:3. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 37].

(2-(4-Fluorophenyl)cyclopropyl)methanol.[34] Yield: 89% (2.02 g), light yellow oil, cis/trans = 4:5. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 34].

(2-(4-Bromophenyl)cyclopropyl)methanol.[36] Yield: 74% (5.72 g), light yellow oil, cis/trans = 4:5. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 36].

(2-(Naphthalen-2-yl)cyclopropyl)methanol.[38] Yield: 89% (2.43 g), yellow oil, cis/trans = 4:5. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 38].

Typical Experimental Procedure for the Preparation of 2-Arylcyclopropane-1-carbaldehydes. A mixture of (2-arylcyclopropyl)methanol (0.12 mol) and pyridinium chlorochromate (PCC) (40.0 g, 0.186 mol) in dry dichloromethane (400 mL) was stirred at room temperature for 4 h. The solution was decanted, and the black solid was washed twice with ether. The mixture was passed through a short silica gel column and solvent was evaporated under reduced pressure to give the desired 2-arylcyclopropanecarbaldehyde as a colorless oil. The product obtained was used without additional purification.

2-Phenylcyclopropane-1-carbaldehyde.[39] Yield: 97% (25.3 g), yellow oil, cis/trans = 3:4. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 39].

2-(4-Methoxyphenyl)cyclopropane-1-carbaldehyde.[39] Yield: 90% (5.15 g), yellow oil, cis/trans = 1:3.5. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 39].

2-(4-Fluorophenyl)cyclopropane-1-carbaldehyde.[39] Yield: 76% (1.51 g), orange oil, cis/trans = 1:1.6. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 39].

2-(4-Bromophenyl)cyclopropane-1-carbaldehyde.[39] Yield: 89% (4.61 g), colorless oil, cis/trans = 1:1.4. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 39].

2-(Naphthalen-2-yl)cyclopropanecarbaldehyde.[39] Yield: 76% (1.83 g), yellow crystals, mp: 68−72 °C, cis/trans = 1:1.6. ^{1}H and $^{13}C\{^{1}H\}$ spectroscopic data are identical to those described in the literature [ref 39].

Synthesis of Starting Cyclopropanes 1a−e. The starting 1,1′-bicyclopropyl-2,2-dicarboxylates **1a−e** (ABCD) were synthesized from the corresponding dimethyl (2-arylcyclopropyl)-methylenemalonates **3a−e** through an adapted standard synthetic procedure of Corey−Chaykovsky reactions.[30] The compounds **3a−e** were prepared from 2-arylcyclopropanecarbaldehydes and dimethyl malonate in the presence of piperidine and acetic acid.[15]

Typical Experimental Procedure for the Preparation of Dimethyl 2′-Aryl-1,1′-bicyclopropane-2,2-dicarboxylates (1a−e). To a stirred suspension of NaH (0.25 g, 10 mmol) in dry DMSO (8 mL) under an argon atmosphere, trimethylsulfoxonium iodide (1.55 g, 7.0 mmol) was added. The mixture was stirred until the gas evolution ceased (30−50 min). Then, a solution of **3** (7.0 mmol) in dry DMSO (4 mL) was added dropwise. The resulting mixture was stirred at room temperature for 4−5 h, poured into H_2O−ice, and extracted with diethyl ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was separated by column chromatography on silica gel (eluent: petroleum ether−AcOEt, 5:1) to afford compound **1** as a mixture of stereoisomers.

*Dimethyl 2′-Phenyl-1,1′-bicyclopropane-2,2-dicarboxylate (**1a**).* Thick yellow oil, 69% (10.77 g), cis/trans = 1:5; for the trans-isomer, the ratio of diastereomers A/B = 1.2:1; for the cis-isomer, the ratio of diastereomers C/D = 1.4:1. The crude product was purified by silica gel column chromatography (eluent: petroleum ether−AcOEt, 5:1). IR ($CHCl_3$) $\bar{\nu}$: 3063, 3027, 3005, 2953, 2906, 2847, 1727, 1605, 1582, 1498, 1437, 1405, 1370, 1332, 1308, 1278, 1214, 1196, 1181, 1131 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{16}H_{18}O_4Na$, 297.1097; found, 297.1108. Trans-**1a**, diastereomer-**A**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−6.95 (m, 5H, Ph), 3.72 and 3.48 (both s, 2 × 3H, 2 OMe), 1.95−1.86 (m, 1H, H(1)), 1.88−1.77 (m, 1H, H(2′)), 1.61−1.52 (m, 2H, $H_2C(3)$), 1.10−0.89 (m, 3H, $H_2C(3',1')$). $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$): δ 170.6 and 168.4 (2 COO), 142.2, 128.3, 125.8 and 125.7 (Ph), 52.6 and 52.5 (2 OMe), 34.2 (C(2)), 31.7 (C(1)), 22.7 (C(2′)), 21.3 (C(1′)), 20.3 (C(3)), 14.7 (C(3′)). Trans-**1a**, diastereomer-**B**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−6.95 (m, 5 H, Ph), 3.71 and 3.52 (both s, 2 × 3H, 2 OMe), 2.03−1.93 (m, 1H, H(1)), 1.82−1.73 (m, 1H, H(2′)), 1.59−1.52 and 1.45−1.38 (both m, 2 × 1H, $H_2C(3)$), 1.15−1.05 (m, 1H, H(1′)), 1.15−0.90 (m, 2H, $H_2C(3')$). $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$): δ 170.6 and 168.2 (2 COO), 142.1, 128.3, 125.8 and 125.7 (Ph), 52.6 and 52.5 (2 OMe), 34.4 (C(2)), 31.2 (C(1)), 21.6 (C(2′)), 20.9 (C(1′)), 19.7 (C(3)), 15.1 (C(3′)). Cis-**1a**, diastereomer-**C**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−6.95 (m, 5H, Ph), 3.79 and 3.57 (both s, 2 × 3H, 2 OMe), 2.20−2.13 (m, 1H, H(2′)), 1.47−1.40 (m, 2H, H(1) and H_a(3)), 1.24−1.18 (m, 1H, H_b(3)), 1.13−1.08 (m, 1H, H(1′)), 0.87−0.81 (m, 2H, $H_2C(3')$). $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$): δ 170.4 and 168.5 (2 COO), 138.4, 129.3, 128.0 and 126.1 (Ph), 52.6 and 52.4 (2 OMe), 33.6 (C(2)), 28.9 (C(1)), 20.9 (C(2′)), 20.6 (C(3)), 16.8 (C(1′)), 9.2 (C(3′)). Cis-**1a**, diastereomer-**D**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−6.95 (m, 5 H, Ph), 3.79 and 3.64 (both s, 2 × 3H, 2 OMe), 2.27−2.18 (m, 1H, H(2′)), 1.59−1.52 and 1.32−1.25 (both m, 2 × 1H, $H_2C(3)$), 1.29−1.23 (m, 1H, H(1)), 1.07−1.02 and 0.92−0.88 (m, 2H, $H_2C(3')$), 0.81−0.76 (m, 1H, H(1′)). $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$): δ 170.4 and 168.6 (2 COO), 138.5, 129.1, 128.3 and 126.2 (Ph), 52.6 and 52.5 (2 OMe), 33.6 (C(2)), 29.0 (C(1)), 21.9 (C(3)), 21.3 (C(2′)), 17.6 (C(1′)), 10.0 (C(3′)).

*Dimethyl 2′-(4-Methoxyphenyl)-1,1′-bicyclopropane-2,2-dicarboxylate (**1b**).* Yellow oil, 48% (1.077 g), cis/trans = 1:5; for the trans-isomer, the ratio of diastereomers A/B ≈ 1.3:1. The crude product was purified by silica gel column chromatography (eluent: petroleum ether−AcOEt, 5:1). IR ($CHCl_3$) $\bar{\nu}$: 3068, 3044, 3036, 3010, 2955, 2911, 2838, 1723, 1613, 1581, 1516, 1459, 1439, 1368 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{17}H_{20}O_5Na$, 327.1203; found, 327.1208. Trans-isomer-A: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (br.d, J = 8.7 Hz, 2H, *O*-Ar), 6.77 (br.d, J = 8.7 Hz, 2H, *m*-Ar), 3.76

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX

(s, 3H, OMe), 3.72 and 3.52 (both s, 2 × 3H, 2 OMe), 2.01−1.95 (m, 1H, H(1)), 1.87−1.70 (m, 1H, H(2′)), 1.61−1.52 (m, 1H, H_a from $H_2C(3)$), 1.49−1.39 (m, 1H, H_b from $H_2C(3)$), 0.95−0.83 (m, 2H, H(3′)), 0.92−0.84 (m, 1H, H(1′)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.7 and 168.5 (2 COO), 157.8 (*p*-Ar), 134.2 (*i*-Ar), 126.9 (*o*-Ar), 113.8 (*m*-Ar), 55.3 (OMe), 52.6 and 52.5 (2 OMe), 34.2 (C(2)), 31.8 (C(1)), 21.9 (C(2′)), 20.7 (C(1′)), 20.3 (C(3)), 14.2 (C(3′)). Trans-isomer-B: ^1H NMR (300 MHz, $CDCl_3$): δ 6.93 (br.d, *J* = 8.7 Hz 2H, *o*-Ar), 6.77 (br.d, *J* = 8.7 Hz, 2H, *m*-Ar), 3.76 (s, 3H, OMe), 3.72 and 3.55 (both s, 2 × 3H, 2 OMe), 1.92−1.88 (m, 1H, H(1)), 1.61−1.52 (m, 1H, H_a from $H_2C(3)$), 1.49−1.39 (m, 1H, H_b from $H_2C(3)$), 1.06−0.96 (m, 1H, H(2′)), 0.95−0.83 (m, 2H, $H_2C(3')$), 0.92−0.84 (m, 1H, H(1′)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.7 and 168.3 (2 COO), 157.9 (*p*-Ar), 134.1 (*i*-Ar), 126.9 (*o*-Ar), 113.8 (*m*-Ar), 55.3 (OMe), 52.64 and 52.55 (2 OMe), 34.4 (C(2)), 31.3 (C(1)), 20.9 (C(2′)), 20.3 (C(3)), 19.8 (C(1′)) 14.7 (C(3′)).

*Dimethyl 2′-(4-Fluorophenyl)-1,1′-bicyclopropane-2,2-dicarboxylate (**1c**).* Colorless oil, 53% (0.642 g), cis/trans = 1:6.5; for the trans-isomer, the ratio of diastereomers A/B ≈ 1.2:1. The crude product was purified by silica gel column chromatography (eluent: petroleum ether−AcOEt, 5:1). IR ($CHCl_3$) $\bar{\nu}$: 3075, 3046, 3028, 3005, 2977, 2893, 1723, 1605, 1514, 1438, 1392, 1370 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{16}H_{17}FO_4Na$, 315.1003; found, 315.1003. Trans-isomer-A: ^1H NMR (300 MHz, $CDCl_3$): δ 7.04−6.83 (m, 5H, Ar), 3.73 and 3.51 (both s, 2 × 3H, 2 OMe), 1.91−1.83 (m, 1H, H(1)), 1.87−1.79 (m, 1H, H(2′)), 1.61−1.51 (m, 1H, H_a from $H_2C(3)$), 1.50−1.39 (m, 1H, H_b from $H_2C(3)$), 1.01−0.87 (m, 2H, H(3′)), 0.92−0.85 (m, 1H, H(1′)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.6 and 168.4 (2 COO), 161.2 (d, *J* = 243 Hz, CF), 137.9 (*i*-Ar), 127.3 (d, *J* = 7.9 Hz, *o*-Ar), 115.1 (d, *J* = 21.3 Hz, *m*-Ar), 52.7 and 52.6 (2 OMe), 34.2 (C(2)), 31.7 (C(1)), 22.0 (C(2′)), 21.2 (C(1′)), 20.4 (C(3)), 14.6 (C(3′)). ^{19}F NMR (282 MHz, $CDCl_3$): δ −118.5 (ddd, *J* = 14.0, 8.5, 5.5 Hz). Trans-isomer-B: ^1H NMR (300 MHz, $CDCl_3$): δ 7.08−6.80 (m, 5H, Ar), 3.72 and 3.54 (both s, 2 × 3H, 2 OMe), 2.00−1.95 (m, 1H, H(1)), 1.79−1.72 (m, 1H H(2′)), 1.61−1.51 (m, 1H, H_a from $H_2C(3)$), 1.50−1.39 (m, 1H, H_b from $H_2C(3)$), 1.08−1.00 (m, H(1′)), 1.01−0.87 (m, 2H, H(3′)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.6 and 168.2 (2 COO), 161.2 (d, *J* = 244 Hz, CF), 137.7 (*i*-Ar), 127.2 (d, *J* = 7.9 Hz, *o*-Ar), 115.1 (d, *J* = 21.3 Hz, *m*-Ar), 52.7 and 52.6 (2 OMe), 34.4 (C(2)), 31.0 (C(1)), 20.9 (C(2′)), 20.7 (C(1′)), 19.6 (C(3)), 15.0 (C(3′)). ^{19}F NMR (282 MHz, $CDCl_3$): δ −118.4 (tt, *J* = 8.3 and 5.6 Hz).

*Dimethyl 2′-(4-Bromophenyl)-1,1′-bicyclopropane-2,2-dicarboxylate (**1d**).* Yellow oil, 59% (1.54 g), cis/trans = 1:5; for the trans-isomer, the ratio of diastereomers A/B ≈ 1.5:1. The crude product was purified by silica gel column chromatography (eluent: petroleum ether−AcOEt, 5:1). IR ($CHCl_3$) $\bar{\nu}$: 3034, 1724, 1492, 1438, 1281 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{16}H_{17}BrO_4Na$, 375.0202 and 377.0183; found, 375.0198 and 377.0182. Trans-isomer-A: ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.4 Hz, 2H, *m*-Ar), 6.87 (d, *J* = 8.4 Hz, 1H, *o*-Ar), 3.73 and 3.50 (both s, 2 × 3H, 2 OMe), 1.84−1.76 and 1.92−1.83 (m, 2 × 1H, H(2′), H(1)), 1.63−1.55 (m, 1H, H_a from $H_2C(3)$), 1.49−1.42 (m, 1H, H_b from $H_2C(3)$), 1.10−0.83 (m, 3H, $H_2C(3')$ and H(1′)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.5 (2 COO), 141.3 (*i*-Ar), 131.3 (*m*-Ar), 127.4 (*o*-Ar), 119.2 (C−Br), 52.7 and 52.6 (2 OMe), 34.1 (C(2)), 31.5 (C(1)), 22.2 (C(2′)), 21.5 (C(1′)), 20.3 (C(3)), 14.9 (C(3′)). Trans-isomer-B: ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (br d, *J* = 8.4 Hz, 2H, *m*-Ar), 6.87 (br d, *J* = 8.4 Hz, 1H, *o*-Ar), 3.73 and 3.54 (both s, 2 × 3H, 2 OMe), 2.01−1.95 (m, 1H, H(2′)), 1.57−1.48 (m, 1H, H_a from $H_2C(3)$), 1.47−1.38 (m, 1H, H_b from $H_2C(3)$), 1.13−0.81 (m, 3H, $H_2C(3')$, H(1′)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.3 (2 COO), 141.1 (*i*-Ar), 131.3 (*m*-Ar), 127.5 (*o*-Ar), 119.3 (C−Br), 52.7 and 52.6 (2 OMe), 34.3 (C(2)), 30.8 (C(1)), 21.08 and 20.98 (C(3′) and C(1′)), 19.5 (C(3)), 15.2 (C(3′)).

*Dimethyl 2′-Naphthalen-2-yl-1,1′-bicyclopropane-2,2-dicarboxylate (**1e**).* Colorless oil, 52% (0.632 g), cis/trans = 1:6; for the trans-isomer, the ratio of diastereomers A/B ≈ 1.6:1. The crude product was purified by silica gel column chromatography (eluent: petroleum ether−AcOEt, 5:1). IR ($CHCl_3$) $\bar{\nu}$: 3046, 3039, 3028, 3005, 2977, 2893, 1723, 1605, 1514, 1458, 1438, 1336 cm^{-1}. HRMS: calcd for $[M + H]^+$ $C_{20}H_{21}O_4$, 325.1438; found, 325.1434. Trans-isomer-A: ^1H NMR (300 MHz, $CDCl_3$): δ 7.91−7.60, 7.47−7.34 and 7.17−7.08 (all m, 3 + 3 + 1H, Ar), 3.74 and 3.44 (both s, 2 × 3H, 2 OMe), 2.03−1.94 (m, 1H, H(1)), 2.09−2.02 (m, 1H, H(2′)), 1.70−1,59 (m, 1H, H_a from $H_2C(3)$), 1.57−1.46 (m, 1H, H_b from $H_2C(3)$), 1.19−1.03 (m, 2H, $H_2C(3')$), 1.12−1.05 (m, 1H, H(1′)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.6 and 168.4 (2 COO), 139.6 (C(2″)), 133.4 and 131.9 (C(4a) and C(8a)), 127.9, 127.6, 127.3, 126.1, 125.0, 124.6 and 123.8 (all CH, Ar), 52.7 and 52.6 (2 OMe), 34.2 (C(2)), 31.8 (C(1)), 22.9 (C(2′)), 21.3 (C(1′)), 20.4 (C(3)), 14.7 (C(3′)). Trans-isomer-B: ^1H NMR (300 MHz, $CDCl_3$): δ 7.91−7.60, 7.47−7.34 and 7.17−7.08 (all m, 3 + 3 + 1H, Ar), 3.73 and 3.51 (both s, 2 × 3H, 2 OMe), 2.11−2.03 (H(1)), 2.02−1.97 (m, 2H, H(2′)), 1.70−1.59 (m, 1H, H_a from $H_2C(3)$), 1.57−1.46 (m, 1H, H_b from $H_2C(3)$), 1.28−1.22 (m, 1H, H(1′)), 1.19−1.03 (m, 2H, $H_2C(3')$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.2 and 168.2 (2 COO), 139.5 (C(2″)), 133.4 and 132.0 (C(4a) and C(8a)), 127.9, 127.6, 127.3, 126.0, 125.1, 124.6 and 123.92 (all CH, Ar), 52.7 and 52.6 (2 OMe), 34.4 (C(2)) 31.2 (C(1)), 21.8 (C(2′)), 20.8 (C(1′)), 19.7 (C(3)), 15.1 (C(3′)).

Typical Experimental Procedure for the Preparation of Dimethyl (2-Arylcyclopropyl)methylenemalonates (3a−e). A solution of 2-arylcyclopropanecarbaldehyde (1 equiv), dimethyl malonate (1 equiv), piperidine (0.1 equiv), and acetic acid (0.1 equiv) in benzene was refluxed in an oil bath with a Dean−Stark attachment for 3 h until water was not obtained. After that, the reaction mixture was first washed with an aqueous solution of HCl (10%) and then with a solution of $NaHCO_3$ (5%). The organic layer was dried over $MgSO_4$ and evaporated. The residue was separated by column chromatography on silica gel (eluent: benzene−AcOEt, 35:1) to afford compound **3** as a colorless or thick orange oil.

*Dimethyl (2-Phenylcyclopropyl)methylenemalonate (**3a**).* The crude product was purified by silica gel column chromatography (eluent: eluent: benzene−AcOEt, 35:1). Thick orange oil (76%, 45.8 g, cis/trans = 1:5). IR ($CHCl_3$) $\bar{\nu}$: 3085, 3062, 3028, 2953, 2904, 2847, 1725, 1630, 1606, 1498, 1458, 1368, 1318, 1305, 1194, 1177 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{15}H_{16}O_4Na$, 283.0941; found, 283.0931. Trans-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.36−7.06 (m, 5H, Ph), 6.58 (d, 1H, *J* = 10.7 Hz, =CH), 3.79 and 3.77 (both s, 2 × 3H, 2 OMe), 2.34−2.21 (m, 2H, HC−CH), 1.60−1.51 and 1.42−1.33 (both m, 2 × 1H, CH_2). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 165.8 and 164.8 (2 COO), 155.0 (=CH), 139.8 (*i*-Ph), 128.6 and 126.3 (*O*- and *m*-Ph), 126.5 (*p*-Ph), 125.1 (=C), 52.3 and 52.2 (2 OMe), 28.0 (CH), 24.9 (CH), 18.7 (CH_2). Cis-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.31−7.05 (m, 5H, Ph), 6.30 (d, 1H, *J* = 11.5 Hz, =CH), 3.85 and 3.64 (both s, 2 × 3H, 2 OMe), 2.73 (ddd, 1H, *J* = 8.4, 8.2 and 8.0 Hz, CHPh), 2.41−2.32 (m, 1H, CH), 1.62−1.54 and 1.43−1.35 (both m, 2 × 1H, CH_2). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 166.2 and 164.3 (2 COO), 152.9 (=CH), 136.8 (*i*-Ph), 129.2 and 128.5 (*O*- and *m*-Ph), 126.9 (*p*-Ph), 126.2 (=C), 52.2 and 52.1 (2 OMe), 27.0 (C(2)), 20.5 (C(1)), 15.2 (CH_2).

*Dimethyl (2-(4-Methoxyphenyl)cyclopropyl)methylenemalonate (**3b**).* The crude product was purified by silica gel column chromatography (eluent: benzene−AcOEt, 35:1). Yield: 43% (3.12 g), yellow oil, cis/trans = 1:5. IR ($CHCl_3$) $\bar{\nu}$: 3075, 3004, 2954, 2838, 1731, 1628, 1614, 1582, 1437, 1397, 1368 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{16}H_{18}O_5Na$, 313.1046; found, 313.1049. Trans-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.03 (br.d, *J* = 8.7 Hz, 2H, *o*-C_6H_4), 6.81 (br.d, *J* = 8.7 Hz, 2H, *m*-C_6H_4), 6.57 (d, *J* = 11.1 Hz, 1H, =CH), 3.81, 3.79 and 3.77 (all s, 3 × 3H, 3 OMe), 2.28 (ddd, *J* = 9.1, 6.3, 4.0 Hz, 1H, CH), 2.23−2.13 (m, 1H, CH), 1.52 (ddd, *J* = 8.3, 6.4, 5.1 Hz, 1H, H_a from CH_2), 1.33 (dt, *J* = 8.8, 5.1 Hz, 1H, H_b from CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 165.9 and 164.8 (2 COO), 158.4 (*p*-Ar), 155.3 (=CH), 131.8 (*i*-Ar), 127.6 (*o*-Ar), 124.8 (=C), 114.0 (*m*-Ar), 55.3 (OMe), 52.3 and 52.2 (2 OMe), 27.5 (C(1)), 24.8 (C(2)), 18.5(C(3)). Cis-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (br.d, *J* = 8.7 Hz, 2H, *o*-C_6H_4), 6.83 (br.d, *J* = 8.7 Hz, 2H, *m*-C_6H_4), 6.30 (d, *J* = 11.4 Hz, 1H, =CH), 3.86, 3.80 and 3.65 (all s, 3

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX

× 3H, 3 OMe), 2.67 (q, J = 7.9 Hz, 1H, CH). The remaining signals overlap with the signals of the major isomer. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 153.4 (=CH), 130.3 and 127.5 (o- and m-Ar), 125.9 (=C), 26.3 (C(1)), 20.4(C(2)), 15.5 (C(3)); other signals are not identified.

*Dimethyl (2-(4-Fluorophenyl)cyclopropyl)methylenemalonate (**3c**).* The crude product was purified by silica gel column chromatography (eluent: benzene–AcOEt, 35:1). Yield: 50% (1.49 g), colorless oil, cis/trans = 1:5.5. IR ($CHCl_3$) $\bar{\nu}$: 3053, 3036, 3029, 2954, 2887, 1724, 1631, 1607, 1513, 1438, 1395, 1367, 1316 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{15}H_{15}FO_4Na$, 301.0847; found, 301.0849. Trans-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.13–6.95 (m, 4H, C_6H_4), 6.56 (d, J = 11.0 Hz, 1H, =CH), 3.80 and 3.77 (both s, 2 × 3H, 2 OMe), 2.43–2.09 (m, 2H, HC–CH), 1.70–1.45 (m, H_a from CH_2), 1.36 (dt, J = 9.1, 5.2 Hz, 1H, H_b from CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 165.9 and 164.8 (2 COO), 161.7 (d, J = 243 Hz, CF), 154.8 (=CH), 135.5 (i-Ar), 128.0 (d, J = 8.0 Hz, o-Ar), 125.3 (=C), 115.5 (d, J = 21.4 Hz, m-Ar), 52.4 and 52.3 (2 OMe), 27.3 (C(2)), 24.7 (C(1)), 18.6 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$): δ −117.03 (tt, J = 8.8, 5.2 Hz). Cis-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 6.23 (d, J = 11.4 Hz, 1H, =CH), 3.87 and 3.68 (both s, 2 × 3H, 2 OMe), 2.68 (q, J = 8.0 Hz, 1H, CH). The remaining signals overlap with the signals of the major isomer. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 166.1 and 165.7 (2 COO), 161.7 (d, J = 243 Hz, CF), 152.6 (=CH), 137.8 (i-Ar), 130.8 (d, J = 8.0 Hz, o-Ar), 126.8 (=C), 115.4 (d, J = 21.3 Hz, m-Ar), 52.41 and 52.37 (2 OMe), 26.1 (C(2)), 20.3 (C(1)), 15.5 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$): δ −116.4 (tt, J = 9.1, 5.3 Hz).

*Dimethyl (2-(4-Bromophenyl)cyclopropyl)methylenemalonate (**3d**).* The crude product was purified by silica gel column chromatography (eluent: benzene–AcOEt, 35:1). Yield: 73% (4.87 g), yellow oil, cis/trans = 1:6. IR ($CHCl_3$) $\bar{\nu}$: 3052, 3041, 3022, 1724, 1632, 1492, 1438 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{15}H_{15}BrO_4Na$, 361.0046 and 363.0026; found, 361.0041 and 363.0025. Trans-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (br.d, J = 8.4 Hz, 2H, o-C_6H_4), 7.00 (br.d, J = 8.4 Hz, 2H, H m-C_6H_4), 6.55 (d, J = 10.5 Hz, 1H, (=CH)), 3.80 and 3.78 (both s, 2 × 3H, 2 OMe), 2.42–2.12 (m, 2H, HC–CH), 1.63–1.47 and 1.44–1.31 (both m, 2 × 1H, CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 165.8 and 164.7 (2 COO), 154.4 (=CH), 138.9 (i-Ar), 131.6 (o-Ar), 128.1 (m-Ar), 125.4 (C=), 120.2 (p-Ar), 52.3 and 52.3 (2 OMe), 27.4 (C(2)), 24.9 (C(1)), 18.6 (C(3)). Cis-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (br.d, J = 8.4 Hz, 2H, o-C_6H_4), 7.11 (d, J = 8.4 Hz, 2H, m-C_6H_4), 6.24 (d, J = 11.1 Hz, 1H, =CH), 3.86 and 3.67 (both s, 2 × 3H, 2 OMe), 2.66 (q, $J \approx$ 8.0 Hz, 1H, HC), 2.42–2.31 (m, 1H, CH). The remaining signals overlap with the signals of the major isomer.

*Dimethyl (2-(Naphthalen-2-yl)cyclopropyl)methylenemalonate (**3e**).* The crude product was purified by silica gel column chromatography (eluent: benzene–AcOEt, 35:1). Yield: 56% (1.55 g), colorless crystals, mp 59–62 °C, cis/trans = 1:7. IR ($CHCl_3$) $\bar{\nu}$: 3050, 3035, 3016, 2954, 2887, 1724, 1631, 1603, 1510, 1438, 1374, 1348, 1309 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{19}H_{18}O_4Na$, 333.1097; found, 333.1098. Trans-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.87–7.73, 7.50–7.31, 7.25–7.20 (all m, 3 + 2 + 1H, Ar), 7.56 (br s, 1H, H(1′)), 6.63 (d, J = 11.1 Hz, =CH), 3.79 and 3.78 (both s, 2 × 3H, 2 OMe), 2.47 (ddd, J = 9.0, 6.3, 4.0 Hz, 1H, CH), 2.35 (dddd, J = 11.1, 8.3, 5.2, 4.0 Hz, 1H, CH), 1.71 (ddd, J = 8.3, 6.3, 5.2 Hz, 1H, H_a from CH_2), 1.44 (dt, J = 9.0, 5.2 Hz, 1H, H_b from CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 165.9 and 164.8 (2 COO), 154.9 (=CH), 137.3 (C(2′)), 133.5 and 132.4 (C(4a) and C(8a)), 128.3, 127.7, 127.5, 127.1, 126.3, 125.6 and 124.8 (all CH, Ar), 124.9 (=C), 52.4 and 52.2 (2 OMe), 28.3 (C(1)), 25.2 (C(2)), 18.7 (C(3)). Cis-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 6.30 (d, J = 11.3 Hz, 1H, =CH), 2.88 (q, $J \approx$ 8.1 Hz, 1H, H(2)). The remaining signals overlap with the signals of the major isomer. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 152.8 (=CH), 27.3 (C(1)), 20.7 (C(2)), 15.4 (C(3)); other signals are not identified.

*Mixture of Dimethyl 2′-(4-Nitrophenyl)-[1,1′-bi(cyclopropane)]-2,2-dicarboxylate (ortho-**1f**) and Dimethyl 2′-(2-Nitrophenyl)-[1,1′-bi(cyclopropane)]-2,2-dicarboxylate (para-**1f**).* To 8.5 mL of acetic anhydride at −50 °C, fuming nitric acid (1.15 g, 18.2 mmol) was added dropwise, followed by the slow addition of **1a** (5 g, 18.2 mmol) solution in acetic anhydride (3 mL). The mixture was stirred at −30 °C for 2 h, poured into hot water (about 60 °C), and extracted with Et_2O three times. The combined organic layers were washed with water and saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo to give a mixture of ortho- and para-isomers of **1f** (5.32 g, 91%, o/p 2.8:1, dr 1.85:1, trans/cis > 12:1) as a yellow oil. The obtained product was used without additional purification. HRMS: calcd for $[M + Na]^+$ $C_{16}H_{17}NO_6Na$, 342.0948; found, 342.0956. Para-trans-isomer, both diastereomers (1.85/1): ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, J = 8.6 Hz, 2H, m-C_6H_4), 7.12 (d, J = 8.6 Hz, 2H, o-C_6H_4), 3.73, 3.68, 3.65, 3.48 (both s, 4 × 3H), 2.40 (ddd, J = 14.5, 9.6, 5.5 Hz, 1H, H(2′)), 1.87 (dt, J = 14.9, 6.1 Hz, 1H, H_a from H(3)), 1.66–1.57 (m, 1H, H_b from H(3)), 1.27–0.81 (m, 3 × 1H, H(3′) and H(1′)). Ortho-trans-isomer, both diastereomers (1.85/1): ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J = 8.1 Hz, 1H, m_a-C_6H_4), 7.47 (t, J = 7.2 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.13–7.05 (m, 1H), 3.73, 3.68, 3.65, 3.48 (both s, 4 × 3H), 2.17–2.06 (m, 1H, H(2′)), 1.69–1.39 (m, 2H, H(3)), 1.27–0.81 (m, 3 × 1H, H(3′) and H(1′)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.3, 168.4, 150.6, 136.6, 132.8, 128.2, 127.9, 126.8, 126.2, 126.0, 124.3, 123.6, 52.8, 52.7, 52.5, 34.3, 34.1, 31.8, 31.2, 30.4, 23.3, 22.9, 22.6, 21.6, 21.0, 20.4, 20.2, 19.9, 19.6, 19.5, 19.3, 13.8, 13.1.

*Dimethyl (E)-2-(5-Iodo-5-phenylpent-2-en-1-yl)malonate (**7a**).* GaI_3 (40 mg, 0.09 mol) was added to the solution of **1a** (80.3 mg, 0.29 mmol) and Bu_4NGaI_4 (239.8 mg, 0.29 mmol) in dry CH_2Cl_2 (3 mL) and the resulting mixture was stirred at room temperature for 2 h. After that, the reaction mixture was treated with 10% HCl and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Silica gel column chromatography (eluent: benzene–AcOEt, 35:1) gave the desired product as a yellow oil (84 mg, 72%). IR ($CHCl_3$) $\bar{\nu}$: 3084, 2956, 2877, 1733, 1461, 1437, 1283, 1187 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{16}H_{19}IO_4Na$, 425.0220; found, 425.0220. ^1H NMR (300 MHz, $CDCl_3$): δ 7.49–7.07 (m, 5H, Ph), 5.64–5.37 (m, 2 H, H(2) and H(3)), 5.06 (t, J = 7.7 Hz, 1H, H(5)), 3.73 and 3.72 (both s, 2 × 3H, 2 OMe), 3.41 (t, J = 7.5 Hz, 1H, CH), 3.02 (ddd, J = 14.1, 8.2 and 6.1 Hz, 1H, H_a from $H_2C(4)$), 2.83 (ddd, J = 14.1, 7.4 and 5.2 Hz, 1H, H_b from $H_2C(4)$), 2.67–2.49 (m, 2H, H(1)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.2 (2 COO), 143.5 (i-Ph), 131.1 and 129.1 (C(2) and C(3)), 128.7 and 127.2 (o- and m-Ph), 128.0 (p-Ph), 52.6 (2 OMe), 51.6 (CH), 44.0 (C(4)), 32.9 (C(5)), 31.7 (C(1)).

*Mixture of Dimethyl (E)-2-(5-Iodo-5-(4-nitrophenyl)pent-2-en-1-yl)malonate (para-**7f**) and Dimethyl (E)-2-(5-Iodo-5-(2-nitrophenyl)pent-2-en-1-yl)malonate (ortho-**7f**).* This compound was obtained analogously to compound **7a** (o/p 1.6/1). HRMS: calcd for $[M + Na]^+$ $C_{16}H_{18}INO_6Na$, 470.0071; found, 470.0067. Yellow oil, 53% (210 mg), o-/p- = 1.7:1. Para-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 8.8 Hz, 2H, m-C_6H_4), 7.52 (d, J = 8.8 Hz, 2H, o-C_6H_4), 5.59–5.32 (m, 2H, H(2) and H(3)), 5.03 (t, J = 7.7 Hz, 1H, H(5)), 3.72 and 3.71 (both s, 2 × 3H, 2 OMe), 3.43–3.33 (m, 1H, CH), 3.11–2.92 (m, 1H, H_a from $H_2C(4)$), 2.83 (dd, J = 14.2 and 6.7 Hz, 1H, H_b from $H_2C(4)$), 2.77–2.43 (m, 2H, H(1)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.1 (2 COO), 150.6 (p-C_6H_4), 147.0 (i-C_6H_4), 130.1 and 130.0 (C(2) and C(3)), 128.2 (o-C_6H_4), 124.0 (m-C_6H_4), 52.6 (2 OMe), 51.4 (CH), 43.4 (C(4)), 31.6 (C(1)), 28.6 (C(5)). Ortho-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.84–7.74 (m, 2 × 1H, o- and m_a-C_6H_4), 7.64–7.55 (m, 1H, p-C_6H_4),7.44–7.34 (m, 1H, m_b-C_6H_4),5.65 (dd, J = 8.2, 6.8 Hz, 1H, H(5)), 5.59–5.32 (m, 3H, H(2) and H(3)), 3.72 and 3.71 (both s, 2 × 3H, 2 OMe), 3.43–3.33 (m, 1H, CH), 3.11–2.92 (m, 1H, H_a from $H_2C(4)$), 2.83 (dd, J = 14.2 and 6.8 Hz, 1H, H_b from $H_2C(4)$), 2.77–2.43 (m, 2H, H(1)). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.1 (2 COO), 147.0 (i-C_6H_4) 133.3 (p-C_6H_4), 130.9 (m_a-C_6H_4),130.1 and 130.0 (C(2) and C(3)), 128.5 (m_b-C_6H_4), 124.6 (o-C_6H_4), 52.6 (2 OMe), 51.4 (CH), 43.7 (C(4)), 31.6 (C(1)), 22.9 (C(5)).

*Dimethyl (E)-2-(5-(4-Bromophenyl)-5-iodopent-2-en-1-yl)-malonate (**7d**).* This compound was obtained analogously to compound **7a**. Yellow oil, 41% (79 mg). HRMS: calcd for [M +

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX–XXX

Na]$^+$ $C_{17}H_{20}O_5Na$, 327.1203; found, 327.1197. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 2H, m-C_6H_4), 7.31−7.20 (m, 2H, o-C_6H_4), 5.48 (dt, J = 12.6, 6.3 Hz, 2H, H(2) and H(3)), 4.99 (t, J = 7.6 Hz, 1H, H(5)), 3.73 and 3.72 (both s, 2 × 3H, 2 OMe), 3.40 (t, J = 7.6 Hz, 1H, CH), 2.97 (dd, J = 14.4, 7.6 Hz, 1H, H_a from $H_2C(4)$), 2.80 (dt, J = 14.0, 6.7 Hz, 1H, H_b from $H_2C(4)$), 2.57 (t, J = 6.8 Hz, 2H, H(1)). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.1 (2 COO), 142.6 (i-C_6H_4), 131.8 (m-C_6H_4), 130.7 and 129.4 (C(2) and C(3)), 128.9 (o-C_6H_4), 121.6 (p-C_6H_4), 52.6 (2 OMe), 51.5 (CH), 43.9 (C(4)), 31.7 (C(1)), 31.0 (C(5)).

*Tetramethyl (E)-9-(4-Bromophenyl)-3-(2-(4-bromophenyl)-cyclopropyl)-9-iodonon-6-ene-1,1,4,4-tetracarboxylate (**8**).* Silica gel column chromatography (eluent: benzene−AcOEt, 35:1) gave the desired product as a yellow oil (33 mg, 20%, dr = 1/1). HRMS: calcd for [M + Na]$^+$ $C_{32}H_{35}Br_2IO_8Na$, 854.9636; found, 854.9626. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.37 (m, 2 × 2H, 2 m-C_6H_4), 7.25−7.21 (m, 2H, o-C_6H_4), 6.99−6.79 (m, 2H, o-C_6H_4), 5.72−5.55 (m, 1H, H(6)), 5.47−5.37 (m, 1H, H(7)), 5.08−4.85 (m, 1H, H(9)), 3.80, 3.72, 3.70 and 3.64 (all s, 4 × 3H, 4 OMe), 3.67−3.62 (m, 1H, H(1)), 3.04−2.91 (m, 1H, H_a from CH_2(8)), 2.81 (dd, J = 13.9, 6.6 Hz, 1H, H_b from CH_2(8)), 2.67 (dd, J = 12.3, 7.1 Hz, 2H, H(5)), 2.36−2.14 (m, 1H, H_a from CH_2(2)), 2.02−1.90 (m, 1H, H_b from CH_2(2)), 1.80−1.68 (m, 1H, H(3)), 1.74−1.64 (m, 1H, CH), 1.06−0.95 (m, 1H, CH), 0.97−0.88 (m, 2H, CH_2). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ170.6, 170.5, 169.6 and 169.5 (4 COO), 142.5 (i-C_6H_4), 141.3 (i-C_6H_4), 131.9 (m-C_6H_4), 131.5 (m-C_6H_4), 131.5 (C(7)), 128.8 (o-C_6H_4), 128.3 (C(6)), 127.2 (o-C_6H_4), 121.6 (p-C_6H_4), 119.3 (p-C_6H_4), 62.5 (C(4)), 52.7 and 52.6 (4 OMe), 49.7 (C(1)), 45.4 (C(3)), 43.9 (C(8)), 37.5 (C(5)), 31.7 (C(2)), 30.9 (C(9)), 25.5 (CH), 22.1 (CH), 15.2 (CH_2).

*Dimethyl 4′-Methoxy-3,6-dihydro-[1,1′-biphenyl]-2,2(1H)-dicarboxylate (**6b**).* This compound was obtained analogously to compound **7a**. Yield: 56% (80 mg), yellow oil. IR ($CHCl_3$) $\bar{\nu}$: 3054, 3046, 2954, 2839, 2401, 1731, 1611, 1554, 1513, 1461, 1436, 1341, 1299, 1283, 1258, 1116 cm^{-1}. HRMS: calcd for [M + Na]$^+$ $C_{17}H_{20}O_5Na$, 327.1203; found, 327.1197. ^{1}H NMR (400 MHz, chloroform-d): δ 7.16 (d, J = 8.7 Hz, 2H, o-C_6H_4), 6.80 (d, J = 8.7 Hz, 2H, m-C_6H_4), 5.92−5.72 (m, 2H, H(5) and H(4)), 3.79 (s, 3H, OMe), 3.83−3.70 (m, 1H, H(1)), 3.70 and 3.62 (both s, 2 × 3H, 2 CO_2Me), 3.03−2.90 (m, 1H, H_a from CH_2(6)), 2.78−2.56 (m, 2H, CH_2(3)), 2.42−2.30 (m, 1H, H_b from CH_2(6)). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d): δ 171.5 and 170.6 (2 COO), 158.6 (C(Ar) at OMe), 134.3 (i-Ar), 129.3 (o-Ar), 127.4 (C(5)), 123.8 (C(4)), 113.6 (m-Ar), 57.4 (C(2)), 55.1 (OMe), 52.7 and 52.2 (2 CO_2Me), 41.5 (C(1)), 30.3 (C(6)), 27.0 (C(3)).

*Dimethyl 2-(7-Chloro-5,7-diphenylhepta-2,6-dien-1-yl)malonate (**9a**).* $GaCl_3$ (142.3 mg, 0.8 mmol) was added to the ice-cooled solution of **1a** (221.5 mg, 0.8 mmol) and phenylacetylene (412.6 mg, 4 mmol) in dry CH_2Cl_2 (8 mL). The resulting mixture was stirred at 0 °C for 1 h, followed by treatment with 10% HCl. Then, the mixture was extracted with CH_2Cl_2, the combined organic phases were dried over $MgSO_4$, and concentrated in vacuo. The residue was separated by column chromatography on silica gel (eluent: petroleum ether−AcOEt, 10:1) yielding 215 mg (65%, 6E/6Z ≈ 10:1) of compound **9a** as a yellow oil. HRMS: calcd for [M + Na]$^+$ $C_{24}H_{25}ClO_4Na$, 435.1334; found, 435.1325. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89−6.88 (m, 10H, 2 Ph), 6.17 (d, J = 10.9 Hz, 1H, H(6)), 5.43−5.36 (m, 2H, H(2) and H(3)), 3.73 (s, 6H, 2 OMe), 3.47 (dt, J = 10.9 and 7.1 Hz, 1H, H(5)), 3.38 (t, J = 7.5 Hz, 1H, CH), 2.63−2.53 (m, 2H, $H_2C(1)$), 2.49−2.34 (m, 2H, $H_2C(4)$). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.3 (2 COO), 143.3 (C(7)), 132.2 (C(6)), 130.4 and 128.5 (C(2) and C(3)), 128.8, 128.7, 128.6, 128.3, 127.6 and 127.3 (2 Ph, C(2) and C(3)), 52.5 (2 OMe), 51.8 (CH), 45.6 C(5), 40.0 C(4), 31.8 C(1).

*Dimethyl 2-(7-Bromo-5,7-diphenylhepta-2,6-dien-1-yl)-malonate (**9b**).* This compound was obtained analogously to compound **9a**. Yield: 45% (147 mg), yellow oil, 6E/6Z ≈ 10:1. IR ($CHCl_3$) $\bar{\nu}$: 3069, 2847, 1732, 1520, 1494, 1286, 1188 cm^{-1}. HRMS: calcd for [M + Na]$^+$ $C_{24}H_{25}BrO_4Na$, 479.0828 and 481.0809; found, 479.0840 and 481.0818. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47−7.20 (m, 10H, 2 Ph), 6.37 (d, J = 10.9 Hz, 1H, CH(6)), 5.45−5.30 (m, 2H, H(2) and H(3)), 3.72 (s, 6H, 2 OMe), 3.44−3.38 (m, 1H, H(5)), 3.37−3.32 (m, 1H, CH), 2.57 (dd, J = 7.3 and 3.9 Hz, 2H, $H_2C(1)$), 2.39 (t, J = 5.9 Hz, 2H, $H_2C(4)$). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.3 (2 COO), 142.9 and 138.8 (2 i-Ph), 136.6 (C(6)), 130.4 and 128.6 (C(2) and C(3)), 128.7, 128.6, 128.3 and 127.3 (o- and m-C from 2 Ph), 127.9 and 126.6 (2 p-Ph), 120.7 (C(7)), 52.5 (2 OMe), 51.8 (CH), 46.7 (C(5)), 39.6 (C(4)), 31.8 (C(1)).

*Dimethyl 2-(5-(4-Bromophenyl)-7-chloro-7-cyclopropylhepta-2,6-dien-1-yl)malonate (**9c**).* This compound was obtained analogously to compound **9a**. Yield: 37% (37 mg), yellow oil, 6E/6Z ≈ 3:1. HRMS: calcd for [M + NH_4]$^+$ $C_{21}H_{28}Br_2NO_4$, 516.0380; found, 516.0366. ^{1}H NMR (400 MHz, chloroform-d): δ 7.44−7.33 (m, 2H, m-Ar), 7.09−6.99 (m, 2H, o-Ar), 5.98 (d, J = 9.7 Hz, 1H, CH(6)), 5.43−5.31 (m, 2H, CH(1) + CH(3)), 3.70 and 3.70 (both s, 2 × 3H, 2 OMe), 3.74−3.68 (m, 1H, CH(5)), 3.39−3.30 (m, 1H, CH), 2.58−2.48 (m, 2H, CH(1)), 2.38−2.29 (m, 2H, CH(4)), 1.73−1.55 (m, 1H, CH(1′)), 0.91−0.61 (m, 4H, 2 CH_2(2′)). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d): δ 169.3 (2 COO), 155.6 (i-Ar), 142.3 (C(7)), 134.0 (CH(6)), 131.6 (m-Ar), 129.3 (CH(2) and CH(3)), 129.1 (o-Ar), 120.1 (p-Ar), 52.5 (2 OMe), 51.7 (CH), 45.1 (CH(5)), 39.6 (CH_2(4)), 31.8 (CH_2(1)), 15.0 (CH(1′)), 7.4 (CH_2(2′)).

*Dimethyl 2-(7-Bromo-5-(4-fluorophenyl)-7-phenylhepta-2,6-dien-1-yl)malonate (**9d**).* This compound was obtained analogously to compound **9a**. Yield: 43% (29 mg), yellow oil, 6E/6Z ≈ 5:1. IR ($CHCl_3$) $\bar{\nu}$: 3054, 3049, 3032, 3022, 3016, 2399, 1733, 1603, 1510, 1438, 1341, 1280, 1183, 1158 cm^{-}. HRMS: calcd for [M + H]$^+$ $C_{24}H_{25}BrFO_4$, 475.0915; found, 475.0929. ^{1}H NMR (300 MHz, chloroform-d): δ 7.54−6.91 (m, 9H, Ph and C_6H_4), 6.30 (d, J = 10.7 Hz, 1H, CH(6)), 5.37−5.29 (m, 2H, H(2) and H(3)), 3.70 and 3.69 (both s, 2 × 3H, 2 OMe), 3.40−3.25 (m, 2H, CH(5) and CH), 2.60−2.44 (m, 2H, CH(1)), 2.37−2.29 (m, 2H, CH(4)). ^{13}C{^{1}H} NMR (75 MHz, chloroform-d): δ 169.3 (2 COO), 161.56 (d, J = 244.8 Hz, p-Ar), 138.7 (i-Ar), 136.4 (C(6)), 134.0 (i-Ph), 130.2 and 128.3 (C(2) and C(3)), 128.8, 128.7 and 128.4 (o-Ph, m-Ph, p-Ph and o-Ar), 121.1 (C(7)), 115.5 (d, J = 21.2 Hz, m-Ar), 52.6 (2 OMe), 51.8 (CH), 45.9 (C(5)), 39.7 (C(4)), 31.9 (C(1)). ^{19}F NMR (282 MHz, chloroform-d): δ −117.1 (tt, J = 8.6, 5.5 Hz).

*Dimethyl 2-(5-(4-Bromophenyl)-7-chloro-7-phenylhepta-2,6-dien-1-yl)malonate (**9e**).* This compound was obtained analogously to compound **9a**. Yield: 48% (64 mg), yellow oil, 6E/6Z ≈ 4.2:1. IR ($CHCl_3$) $\bar{\nu}$: 3065, 3051, 3046, 3014, 2409, 2393, 1733, 1489, 1438, 1342, 1280, 1183 cm^{-1}. HRMS: calcd for [M + H]$^+$ $C_{24}H_{26}Br_2O_4$, 535.0114; found, 535.0127. ^{1}H NMR (400 MHz, chloroform-d): δ 7.56−6.95 (m, 9H, Ph and C_6H_4), 6.32 (d, J = 10.7 Hz, 1H, CH(6)), 5.40−5.31 (m, 2H, H(2) and H(3)), 3.73 and 3.72 (both s, 2 × 3H, 2 OMe), 3.42−3.28 (m, 3H, CH_2(5) and CH), 2.63−2.49 (m, 2H, CH_2(1)), 2.39−2.33 (m, 2H, CH_2(4)). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d): δ 169.3 (2 COO), 142.0 (i-Ar), 138.6 (C(7)), 135.9 (C(6)), 131.8 (o-Ar), 129.9 C(3), 129.4 (p-Ph), 129.0 (m-Ar), 128.8 and 128.4 (o-Ph and m-Ph), 128.3 (C(2)), 121.3 (i-Ph), 120.3 (CBr), 52.7 and 52.5 (2 OMe), 51.7 (CH), 46.1 C(5), 39.5 C(4), 31.8 (C(1).

*Mixture of Dimethyl 2-(4-(4-Bromophenyl)-2-phenylcyclopent-2-en-1-yl)cyclopropane-1,1-dicarboxylate (**11a**) and Dimethyl (2SR)-2-((1SR,2SR)-4-(4-Bromophenyl)-2-phenylcyclopentyl)-cyclopropane-1,1-dicarboxylate (Hydrogenated Analogue of **11a** via Ionic Hydrogenation).* Minor products during the synthesis of **9e**. Ratio: 2/1. Compound **11a.** Yield 10%, yellow oil, dr 1.75/1. ^{1}H NMR (400 MHz, chloroform-d): δ 7.82−6.86 (m, 9H, Ar), 4.07−3.89 (m, 1H, H(4)), 3.80 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.08−2.87 (m, 1H, H(1)), 2.71 (dt, J = 13.4, 8.7 Hz, 1H, H(5)), 1.99−1.81 (m, 1H, CH), 1.82−1.74 (m, 1H, CH, H(5′)), 1.74−1.68 (m, 1H, H_a from CH_2), 1.40−1.33 (m, 1H, H_b from CH_2). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 131.6, 131.5, 129.2, 129.0, 128.8, 128.7, 128.5, 128.5, 128.3, 127.5, 127.2, 126.8 (Ar), 49.4 (C(4)), 45.9 (C(1)), 40.7 (C(5)), 35.2 (CH), 23.6 (CH_2). Other signals are very small or overlap with the signals of the minor compound and cannot be exactly identified. Hydrogenated analogue of **11a.** Yield 5%, dr 3/1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82−6.86 (m, 9H, Ar), 4.19 (t, J = 8.1 Hz, 1H,

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX

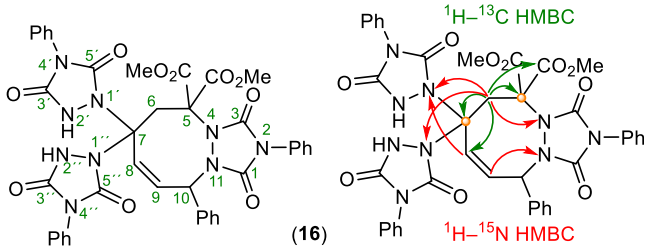
H(4)), 3.83 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.57−2.42 (m, 1H, H(5)), 2.12−1.97 (m, 1H, CH), 2.03−1.99 (m, 1H, H(5′)), 1.81−1.63 (m, 1H, H_a from CH_2), 1.38−1.33 (m, 1H, H_b from CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 131.6, 131.5, 129.2, 129.0, 128.8, 128.7, 128.5, 128.5, 128.3, 127.5, 127.2, 126.8 (Ar), 52.6 (C(4)), 45.3 (C(1)), 41.9 (C(5)), 33.5 (CH), 22.7 (CH_2). Other signals are very small or overlap with the signals of major compound and cannot be exactly identified.

*Mixture of Dimethyl 2-(2-(4-(tert-Butyl)phenyl)-4-phenylcyclopent-2-en-1-yl)cyclopropane-1,1-dicarboxylate (**9f**) and Dimethyl 2-(7-(4-(tert-Butyl)phenyl)-7-chloro-5-phenylhepta-2,6-dien-1-yl)-malonate (**11b**).* This mixture was obtained analogously to compound **9a**. Yield: 36% (for **11b**, 56 mg, dr 1.6/1) and 20% (for **9f**, 34 mg, 6*E*/6*Z* 4.4/1), yellow oil. HRMS: calcd for $[M + Na]^+$ $C_{28}H_{32}O_4Na$, 455.2193; found, 455.2200. Compound **11b**, major diastereomer. ^1H NMR (400 MHz, chloroform-*d*): δ 7.60−7.08 (m, 9H, Ar), 6.04 (t, *J* = 2.1 Hz, 1H, CH(3′)), 4.01 (ddt, *J* = 9.3, 7.1, 2.3 Hz, 1H, CH(4′)), 3.84 and 3.66 (both s, 2 × 3H, 2 OMe), 3.06−2.95 (m, 1H, CH(1′)), 2.72 (dt, *J* = 13.4, 8.6 Hz, 1H, CH_a from 5′), 1.95 (ddd, *J* = 10.6, 9.0, 8.0 Hz, 1H, CH(4)), 1.88−1.74 (m, 2H, H_b from CH_2(5′) and H_a from CH(3)), 1.47−1.40 (m, 1H, CH_b from CH_2(3)), 1.38 (s, 9H, *t*-Bu). Compound **11b**, minor diastereomer. ^1H NMR (400 MHz, chloroform-*d*): δ 7.60−7.08 (m, 9H, Ar), 6.18−6.14 (m, 1H, CH(3′)), 4.24 (tt, *J* = 8.2, 2.1 Hz, 1H, CH(4′)), 3.81 and 3.77 (both s, 2 × 3H, 2 OMe), 3.58−3.49 (m, 1H, CH(1′)), 2.52 (ddd, *J* = 13.1, 7.8, 2.1 Hz, 1H, H_a from CH(5′)), 2.14−2.03 (m, 2H, H_b from 5′ and CH(4)), 1.88−1.79 (m, 1H, H_a from CH(3)), 1.47−1.40 (m, 1H, CH_b from CH_2(3)), 1.38 (s, 9H, *t*-Bu). Compound **9f**. ^1H NMR (400 MHz, chloroform-*d*): δ 6.14 (d, *J* = 11.0 Hz, 1H), 5.39 (qd, *J* = 3.7, 1.8 Hz, 2H), 3.73 (d, *J* = 3.6 Hz, 5H). Other signals are very small or overlap with the signals of major compound and cannot be exactly identified.

Typical Procedure for the Reaction of Cyclopropanes 1a−e with PTAD. $Yb(OTf)_3$ (41 mg, 0.07 mmol) was added to the solution of **1** (0.65 mmol) and PTAD (265 mg, 1.51 mmol) in 5−6 mL of dry DCE. The resulting mixture was stirred at 60 °C (in an oil bath) for 2−5.5 h, followed by treatment with 10% HCl. The mixture was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Silica gel column chromatography (eluent: $CHCl_3$−MeOH, 25:1) gave the desired product **12**.

*Dimethyl 2-((1,3-Dioxo-2,8-diphenyl-2,3,5,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-5-yl)methyl)-2-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)malonate (**12a**).* Reaction time: 2 h, yield: 60% (250 mg), yellow oil, cis/trans ≈ 3.5:1. The crude product was purified by silica gel column chromatography (eluent: $CHCl_3$−MeOH, 25:1). IR ($CHCl_3$) $\bar{\nu}$: 3068, 3036, 3012, 2958, 2849, 1727, 1599, 1503, 1421, 1235 cm^{-1}. HRMS: calcd for $[M + H]^+$ $C_{32}H_{29}N_6O_8$, 625.2041; found, 625.2037. Cis-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 9.55 (s, 1H, NH), 7.54−7.32 (m, 15H, 3 Ph), 6.08 (ddd, *J* = 10.7, 3.4, 1.7 Hz, 1H, H(6)), 5.97 (ddd, *J* = 10.7, 3.7, 1.4 Hz, 1H, H(7)), 5.55−5.46 (m, 1H, H(8)), 5.23−5.08 (m, 1H, H(5)), 3.91 and 3.87 (both s, 2 × 3H, 2 OMe), 3.06 (s, 2H, CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.4 and 166.1 (2 COO), 156.8, 153.9, 152.9 and 151.0 (4 C═O), 136.2, 131.0 and 130.5 (3 *i*-Ph), 129.3, 129.1, 129.0, 128.8, 128.5 and 128.0 (*o*- and *m*-C from 3 Ph), 128.6, 128.4 and 125.9 (3 *p*-Ph), 125.3 and 125.2 (C(6) and C(7)), 72.5 (C), 57.8 (C(8)), 54.1 and 54.0 (2 OMe), 49.9 (C(5)), 37.8 (CH_2). $^{15}N\{^1H\}$ NMR (30.4 MHz, $CDCl_3$, reconstructed from 2D $^1H-^{15}N$ HSQC and HMBC spectra): δ 150.4 and 148.2 (N(2) and N(4′)), 133.8 (N(9), 131.9 (N(4)), 127.2 (N(1′)), 124.3 (N(2′)).

*Dimethyl (Z)-7,7-Bis(3,5-dioxo-4-Phenyl-1,2,4-triazolidin-1-yl)-1,3-dioxo-2,10-diphenyl-2,3,7,10-tetrahydro-1H-[1,2,4]triazolo[1,2-a][1,2]diazocine-5,5(6H)-dicarboxylate (**16**).* Compound **16** is a minor product, less stable under reaction conditions and on SiO_2, and decomposes during isolation attempts; it was analyzed directly in the reaction mixtures using complex $^1H/^{13}C/^{15}N$ NMR spectral data. HRMS (from the reaction mixture) calcd for $[M + K]^+$ $C_{40}H_{33}N_9O_{10}$, 838.1982; found, 838.1947. ^1H NMR (300.1 MHz, $CDCl_3$, from the



reaction mixture, key signals only): δ 6.43 (dd, 1H, ═CH(9), ^3J = 9.9 and 4.9 Hz), 6.03 (ddd, 1H, ═CH(8), ^3J = 9.9 Hz, ^4J = 2.5 and 1.7 Hz), 5.80 (dd, 1H, CH(10)Ph, ^3J = 4.9 Hz, ^4J = 1.7 Hz), 4.70 (d, 1H, CH_2(6)-*a*, ^2J = 14.8 Hz), 3.60 (dd, 1H, CH_2(6)-*b*, ^2J = 14.8 Hz, ^4J = 2.5 Hz), other signals are overlapped. $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, from the reaction mixture, key signals only): δ 130.3 (═CH(9)), 122.3 (═CH(8)), 76.0 (C(7)), 69.5 (C(5)), 56.2 (CH(10)Ph), 49.9 (CH_2(6)), other signals are overlapped. $^{15}N\{^1H\}$ NMR (30.4 MHz, $CDCl_3$, reconstructed from 2D $^1H-^{15}N$ HMBC spectra, accuracy: ±0.2−0.3 ppm, from the reaction mixture, key signals only): δ 138.0 and 137.5 (N(1′) and N(1″)), 134.0 (N(11)), 104.0 (N(4)), other signals are overlapped.

*Dimethyl 2-(3,5-Dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-(8-(4-methoxyphenyl)-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1H-[1,2,4]-triazolo[1,2-a]pyridazin-5-yl)methylmalonate (**12b**).* Reaction time: 2 h, yield: 54% (108 mg), yellow oil, cis/trans ≈ 8:1. The crude product was purified by silica gel column chromatography (eluent: $CHCl_3$−MeOH, 35:1). IR ($CHCl_3$) $\bar{\nu}$: 3046, 3036, 3012, 2956, 2841, 1741, 1611, 1504, 1458, 1412, 1216 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{33}H_{30}N_6O_9Na$, 677.1966; found, 677.1955. ^1H NMR (300 MHz, $CDCl_3$): δ 9.58 (s, 1H, NH), 7.68−7.31 (m, 14H, 2 Ph and C_6H_4), 6.06 (ddd, *J* = 10.4, 3.4, 1.7 Hz, 1H, H(6)), 5.91−6.06 (m, 1H, H(7)), 5.47 (dd, *J* = 4.0, 2.0 Hz, 1H, H(8)), 5.22−5.13 (m, 1H, H(5)), 3.91 and 3.87 (both s, 2 × 3H, 2 OMe), 3.80 (s, 3H, OMe), 3.11−2.96 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 166.5 and 166.1 (2 COO), 160.1 (*i*-Ar), 156.8, 153.9, 153.0 and 151.0 (4 C═O), 131.0, 130.5, 130.0 (3 *i*-Ar), 129.6, 129.3, 129.1, 128.9 and 128.7 (*o*- and *m*-C from 2 Ph and *o*-Ar), 128.4 and 128.0 (2 *p*-Ph), 125.3 and 125.1 (C(6) and C(7)), 114.3 (*m*-Ar), 72.4 (C), 57.2 (C(8)), 55.3 (OMe), 54.2 and 54.0 (2 OMe), 50.1 (C(5)), 37.7 (CH_2).

*Dimethyl 2-(3,5-Dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-(8-(4-fluorophenyl)-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1H-[1,2,4]-triazolo[1,2-a]pyridazin-5-yl)methylmalonate (**12c**).* Reaction time: 2 h, yield: 45% (95 mg), yellow oil, cis/trans ≈ 8:1. The crude product was purified by silica gel column chromatography (eluent: $CHCl_3$−MeOH, 25:1). IR ($CHCl_3$) $\bar{\nu}$: 3043, 3029, 3023, 3011, 1726, 1606, 1504, 1458, 1427, 1288, 1243 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{32}H_{27}FN_6O_8Na$, 665.1767; found, 665.1758. ^1H NMR (300 MHz, $CDCl_3$): δ 9.48 (s, 1H, NH), 7.61−7.33 (m, 14H, 2 Ph and C_6H_4), 6.13 (ddd, *J* = 10.4, 3.6 and 1.9 Hz, 1H, H(6)), 5.96 (ddd, *J* = 10.4, 3.9, 1.8 Hz, 1H, H(7)), 5.50 (dd, *J* = 3.9, 1.9 Hz, 1H, H(8)), 5.24−5.09 (m, 1H, H(5)), 3.93 and 3.89 (both s, 2 × 3H, 2 OMe), 3.12−3.07 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 166.4 and 166.1 (2 COO), 163.0 (d, ^1J = 248 Hz, C−F), 156.8, 153.8, 152.9 and 151.2 (4 C═O), 131.0, 130.4, 130.1 (3 *i*-Ar), 130.0, 129.3, 129.2, 128.7 and 128.5 (*o*- and *m*-C from 2 Ph and *o*-Ar), 126.0 and 125.3 (C(6) and C(7)), 116.0 (d, ^2J = 21.7 Hz, *m*-Ar), 72.4 (C), 57.2 (C(8)), 54.2 and 54.0 (2 OMe), 50.0 (C(5)), 37.8 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$): δ −113.00 (tt, *J* = 8.5, 5.1 Hz).

*Dimethyl 2-(8-(4-Bromophenyl)-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1H-[1,2,4]triazolo-[1,2-a]pyridazin-5-yl)methyl-2-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)malonate (**12d**).* Reaction time: 5.5 h, yield: 48% (170 mg), yellow oil, cis/trans ≈ 4.5:1. The crude product was purified by silica gel column chromatography (eluent: CH_2Cl_2−MeOH, 10:1). IR ($CHCl_3$) $\bar{\nu}$: 3053, 1948, 1728, 1599, 1503, 1485, 1427, 1277 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{32}H_{27}BrN_6O_8Na$, 725.0966 and 727.0948; found, 725.0949 and 727.0969. ^1H NMR (300 MHz, $CDCl_3$): δ 9.43 (s, 1H, NH), 7.60−7.28 (m, 14H, 2 Ph and C_6H_4), 6.11 (ddd, *J* = 10.5, 3.7, 1.9 Hz, 1H,

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX

H(6)), 5.90 (ddd, J = 10.5, 3.8, 1.8 Hz, 1H, H(7)), 5.45−5.39 (m, 1H, H(8)), 5.22−5.08 (m, 1H, H(5)), 3.90 and 3.86 (both s, 2 × 3H, 2 OMe), 3.08−3.00 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 166.4 and 166.1 (2 COO), 156.7, 153.9, 152.7 and 151.4 (4 C═O), 135.3, 132.2 and 130.9 (3 *i*-Ar), 130.4, 130.2, 129.8, 129.3, 129.2 and 129.0 (3 *o*- and *m*-Ar), 129.1 and 128.5 (2 *p*-Ph), 126.0 and 125.3 (C(6) and C(7)), 122.2 (C−Br), 72.5 (C(6)), 57.4 (C(1)), 54.2 and 54.1 (2 OMe), 49.8 (C(5)), 37.7 (CH_2).

*Dimethyl 2-(3,5-Dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-(8-(naphthalen-2-yl)-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-5-yl)methylmalonate (**12e**).* Reaction time: 5.5 h, yield: 22% (81 mg), yellow oil, cis/trans ≈ 10:1. The crude product was purified using silica gel column chromatography (eluent: $CHCl_3$−MeOH, 25: 1). IR ($CHCl_3$) $\bar{\nu}$: 3064, 2847, 1949, 1726, 1600, 1503, 1458, 1425, 1280 cm^{-1}. HRMS: calcd for $[M + Na]^+$ $C_{36}H_{30}N_6O_8Na$, 697.2017; found, 697.2004. ^1H NMR (300 MHz, $CDCl_3$): δ 9.65 (s, 1H, NH), 8.06−7.12 (m, 17H, 2 Ph and naphthyl), 6.26−6.08 (m, 1H, H(6)), 6.10−6.01 (m, 1H, H(7)), 5.74−5.64 (m, 1H, H(8)), 5.27−5.17 (m, 1H, H(5)), 3.95 and 3.91 (both s, 2 × 3H, 2 OMe), 3.20−3.11 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 166.8 and 166.1 (2 COO), 156.0, 153.1, 152.4 and 151.3 (4 C═O), 133.6, 133.0, 131.5, 129.3, 129.1, 128.4, 128.2, 126.1, 126.0, 125.7, 125.6, 125.3 and 125.1 (3 Ar and C═C), 72.5 (C), 58.1 (C(8)), 54.2 and 54.0 (2 OMe), 50.0 (C(5)), 37.8 (CH_2).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02293.

Copies of ^1H, ^{13}C, ^{15}N, and 2D NMR spectra for isolated products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Roman A. Novikov − *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation;* orcid.org/0000-0002-3740-7424; Email: novikovfff@bk.ru

Yury V. Tomilov − *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation;* orcid.org/0000-0002-3433-7571; Email: tom@ioc.ac.ru

Authors

Konstantin V. Potapov − *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

Dmitry A. Denisov − *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

Valeriia V. Glushkova − *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02293

Author Contributions

†K.V.P., D.A.D., and R.A.N. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the grant of the Russian Science Foundation (RSF grant no. 19-73-10210). High-resolution mass spectra were recorded in the Department of Structural Studies of N. D. Zelinsky Institute of Organic Chemistry RAS, Moscow.

■ REFERENCES

(1) Reissig, H.-U.; Zimmer, R. Donor−Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1151.

(2) Tomilov, Y. V.; Menchikov, L. G.; Novikov, R. A.; Ivanova, O. A.; Trushkov, I. V. Methods for the synthesis of donor-acceptor cyclopropanes. *Russ. Chem. Rev.* **2018**, *87*, 201.

(3) (a) Carson, C. A.; Kerr, M. A. Heterocycles from cyclopropanes: applications in natural product synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3051. (b) Schneider, T. F.; Kaschel, J.; Werz, D. B. A new golden age for donor−acceptor cyclopropanes. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504. (c) De Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. Cyclization and annulation reactions of nitrogen-substituted cyclopropanes and cyclobutanes. *Chem. Commun.* **2014**, *50*, 10912. (d) Cavitt, M. A.; Phun, L. H.; France, S. Intramolecular donor−acceptor cyclopropane ring-opening cyclizations. *Chem. Soc. Rev.* **2014**, *43*, 804. (e) Grover, H. K.; Emmett, M. R.; Kerr, M. A. Carbocycles from donor−acceptor cyclopropanes. *Org. Biomol. Chem.* **2015**, *13*, 655.

(4) (a) Budynina, E.; Ivanov, K.; Sorokin, I.; Melnikov, M. Ring opening of donor−acceptor cyclopropanes with N-nucleophiles. *Synthesis* **2017**, *49*, 3035. (b) Pagenkopf, B. L.; Vemula, N. Cycloadditions of Donor−Acceptor Cyclopropanes and Nitriles. *Eur. J. Org. Chem.* **2017**, 2561. (c) Meazza, M.; Guo, H.; Rios, R. Synthetic applications of vinyl cyclopropane opening. *Org. Biomol. Chem.* **2017**, *15*, 2479−2490. (d) Ivanova, O. A.; Trushkov, I. V. Donor-Acceptor Cyclopropanes in the Synthesis of Carbocycles. *Chem. Rec.* **2019**, *19*, 2189. (e) Kreft, A.; Lücht, A.; Grunenberg, J.; Jones, P. G.; Werz, D. B. Kinetic Studies of Donor−Acceptor Cyclopropanes: The Influence of Structural and Electronic Properties on the Reactivity. *Angew. Chem., Int. Ed.* **2019**, *58*, 1955−1959. (f) Werz, D. B.; Biju, A. T. Uncovering the Neglected Similarities of Arynes and Donor−Acceptor Cyclopropanes. *Angew. Chem., Int. Ed.* **2020**, *59*, 3385−3398.

(5) (a) Guin, A.; Rathod, T.; Gaykar, R. N.; Roy, T.; Biju, A. T. Lewis Acid Catalyzed Ring-Opening 1,3-Aminothiolation of Donor−Acceptor Cyclopropanes Using Sulfenamides. *Org. Lett.* **2020**, *22*, 2276−2280. (b) Li, B. Q.; Qiu, Z.-W.; Ma, A.-J.; Peng, J.-B.; Feng, N.; Du, J.-Y.; Pan, H.-P.; Zhang, X.-Z.; Xu, X.-T. Diastereoselective Synthesis of Cycloheptannelated Indoles via Lewis-Acid-Catalyzed (4 + 3)-Cyclization of Donor−Acceptor Cyclopropanes. *Org. Lett.* **2020**, *22*, 1903−1907. (c) Chen, D.-F.; Chrisman, C. H.; Miyake, G. M. Bromine Radical Catalysis by Energy Transfer Photosensitization. *ACS Catal.* **2020**, *10*, 2609−2614. (d) Zhang, X.; Feng, M.; Yang, G.; Chai, Z. Sc(OTf) 3 -Catalyzed Chemodivergent Annulations of γ-Butyrolactone-Fused Cyclopropanes with Anthranils. *J. Org. Chem.* **2020**, *85*, 430−440. (e) Boichenko, M. A.; Andreev, I. A.; Chagarovskiy, A. O.; Levina, I. I.; Zhokhov, S. S.; Trushkov, I. V.; Ivanova, O. A. Ring Opening of Donor−Acceptor Cyclopropanes with Cyanide Ion and Its Surrogates. *J. Org. Chem.* **2020**, *85*, 1146−1157. (f) Tamilarasan, V. J.; Srinivasan, K. AlCl 3 -Promoted Ritter-Type Ring-Opening Reactions of γ-Butyrolactone Fused Donor-Acceptor Cyclopropanes with Wet Aliphatic Nitriles. *Eur. J. Org. Chem.* **2020**, 593−598.

(6) (a) Augustin, A. U.; Merz, J. L.; Jones, P. G.; Młostoń, G.; Werz, D. B. (4 + 3)-Cycloaddition of Donor−Acceptor Cyclopropanes with Thiochalcones: A Diastereoselective Access to Tetrahydrothiepines. *Org. Lett.* **2019**, *21*, 9405−9409. (b) Singh, K.; Bera, T.; Jaiswal, V.; Biswas, S.; Mondal, B.; Das, D.; Saha, J. Lewis Acid Catalyzed Nucleophilic Ring Opening and 1,3-Bisfunctionalization of Donor−Acceptor Cyclopropanes with Hydroperoxides: Access to Highly Functionalized Peroxy/(α-Heteroatom Substituted)Peroxy Compounds. *J. Org. Chem.* **2019**, *84*, 710−725. (c) Luo, W.; Sun, Z.; Fernando, E. H. N.; Nesterov, V. N.; Cundari, T. R.; Wang, H.

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX

Asymmetric Ring-Opening of Donor−Acceptor Cyclopropanes with Primary Arylamines Catalyzed by a Chiral Heterobimetallic Catalyst. *ACS Catal.* **2019**, *9*, 8285−8293. (d) Augustin, A. U.; Jones, P. G.; Werz, D. B. Ring-Opening 1, 3-Aminochalcogenation of Donor-Acceptor Cyclopropanes: A Three-Component Approach. *Chem.—Eur. J.* **2019**, *25*, 11620−11624. (e) Singh, K.; Pramanik, S.; Hamlin, T. A.; Mondal, B.; Das, D.; Saha, J. Lewis acid catalyzed annulation of spirocyclic donor−acceptor cyclopropanes with exo-heterocyclic olefins: access to highly functionalized bis-spirocyclopentane oxindole frameworks. *Chem. Commun.* **2019**, *55*, 7069−7072. (f) Akaev, A. A.; Melnikov, M. Y.; Budynina, E. M. Chameleon-Like Activating Nature of the Spirooxindole Group in Donor−Acceptor Cyclopropanes. *Org. Lett.* **2019**, *21*, 9795−9799.

(7) (a) Augustin, A. U.; Busse, M.; Jones, P. G.; Werz, D. B. Formal Insertion of Thioketenes into Donor−Acceptor Cyclopropanes by Lewis Acid Catalysis. *Org. Lett.* **2018**, *20*, 820. (b) Richmond, E.; Vuković, V. D.; Moran, J. Nucleophilic ring opening of Donor−Acceptor cyclopropanes catalyzed by a Brønsted Acid in hexafluoroisopropanol. *Org. Lett.* **2018**, *20*, 574. (c) Dey, R.; Kumar, P.; Banerjee, P. Lewis Acid Catalyzed Annulation of Cyclopropane Carbaldehydes and Aryl Hydrazines: Construction of Tetrahydropyridazines and Application Toward a One-Pot Synthesis of Hexahydropyrrolo[1,2-b]pyridazines. *J. Org. Chem.* **2018**, *83*, 5438−5449. (d) Irwin, L. C.; Renwick, C. R.; Kerr, M. A. Nucleophilic Opening of Donor−Acceptor Cyclopropanes with Indoles via Hydrogen Bond Activation with 1,1,1,3,3,3-Hexafluoroisopropanol. *J. Org. Chem.* **2018**, *83*, 6235−6242. (e) Matsumoto, Y.; Nakatake, D.; Yazaki, R.; Ohshima, T. An Expeditious Route to trans-Configured Tetrahydrothiophenes Enabled by $Fe(OTf)_3$-Catalyzed [3+2] Cycloaddition of Donor−Acceptor Cyclopropanes with Thionoesters. *Chem.—Eur. J.* **2018**, *24*, 6062−6066. (f) Chagarovskiy, A. O.; Vasin, V. S.; Kuznetsov, V. V.; Ivanova, O. A.; Rybakov, V. B.; Shumsky, A. N.; Makhova, N. N.; Trushkov, I. V. (3 + 3)-Annulation of Donor−Acceptor Cyclopropanes with Diaziridines. *Angew. Chem., Int. Ed.* **2018**, *57*, 10338−10342.

(8) (a) Das, S.; Daniliuc, C. G.; Studer, A. Stereospecific 1, 3-Aminobromination of Donor−Acceptor Cyclopropanes. *Angew. Chem., Int. Ed.* **2017**, *56*, 11554. (b) Dey, R.; Banerjee, P. Lewis Acid Catalyzed Diastereoselective Cycloaddition Reactions of Donor−Acceptor Cyclopropanes and Vinyl Azides: Synthesis of Functionalized Azidocyclopentane and Tetrahydropyridine Derivatives. *Org. Lett.* **2017**, *19*, 304. (c) Preindl, J.; Chakrabarty, S.; Waser, J. Dearomatization of electron poor six-membered N-heterocycles through [3 + 2] annulation with aminocyclopropanes. *Chem. Sci.* **2017**, *8*, 7112−7118. (d) Augustin, A. U.; Sensse, M.; Jones, P. G.; Werz, D. B. Stereospecific Reactions of Donor−Acceptor Cyclopropanes with Thioketones: Access to Highly Substituted Tetrahydrothiophenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 14293−14296. (e) Garve, L. K. B.; Jones, P. G.; Werz, D. B. Ring-Opening 1-Amino-3-aminomethylation of Donor−Acceptor Cyclopropanes via 1, 3-Diazepanes. *Angew. Chem., Int. Ed.* **2017**, *56*, 9226.

(9) (a) Sherry, B. D.; Fürstner, A. Iron-Catalyzed Addition of Grignard Reagents to Activated Vinyl Cyclopropanes. *Chem. Commun.* **2009**, 7116−7118. (b) Dieskau, A. P.; Holzwarth, M. S.; Plietker, B. Fe-Catalyzed Allylic C-C-Bond Activation: Vinylcyclopropanes as Versatile A1,A3,D5-Synthons in Traceless Allylic Substitutions and [3 + 2]-Cycloadditions. *J. Am. Chem. Soc.* **2012**, *134*, 5048−5051. (c) Niu, H.-Y.; Du, C.; Xie, M.-S.; Wang, Y.; Zhang, Q.; Qu, G.-R.; Guo, H.-M. Diversity-Oriented Synthesis of Acyclic Nucleosides via Ring-Opening of Vinyl Cyclopropanes with Purines. *Chem. Commun.* **2015**, *51*, 3328−3331. (d) Trost, B. M.; Bai, W.-J.; Hohn, C.; Bai, Y.; Cregg, J. J. Palladium-Catalyzed Asymmetric Allylic Alkylation of 3-Substituted 1 H -Indoles and Tryptophan Derivatives with Vinylcyclopropanes. *J. Am. Chem. Soc.* **2018**, *140*, 6710−6717.

(10) (a) Wang, J.; Dai, Z.; Xiong, C.; Zhu, J.; Lu, J.; Zhou, Q. Palladium-Catalyzed Allylic Alkylation of Aldimine Esters with Vinylcyclopropanes to Yield α,A-Disubstituted A-Amino Acid Derivatives. *Adv. Synth. Catal.* **2019**, *361*, 5105−5111. (b) Tanaka, R.; Tanimoto, I.; Kojima, M.; Yoshino, T.; Matsunaga, S. Imidate as the Intact Directing Group for the Cobalt-Catalyzed C−H Allylation. *J. Org. Chem.* **2019**, *84*, 13203−13210. (c) Hu, Z.; Hu, X.-Q.; Zhang, G.; Gooßen, L. J. Ring-Opening Ortho -C−H Allylation of Benzoic Acids with Vinylcyclopropanes: Merging Catalytic C−H and C−C Activation Concepts. *Org. Lett.* **2019**, *21*, 6770−6773. (d) Ivanova, O. A.; Chagarovskiy, A. O.; Shumsky, A. N.; Krasnobrov, V. D.; Levina, I. I.; Trushkov, I. V. Lewis Acid Triggered Vinylcyclopropane−Cyclopentene Rearrangement. *J. Org. Chem.* **2018**, *83*, 543−560.

(11) Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. A New Type of Donor−Acceptor Cyclopropane Reactivity: The Generation of Formal 1,2-and 1,4-Dipoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 3187.

(12) (a) Zotova, M. A.; Novikov, R. A.; Shulishov, E. V.; Tomilov, Y. V. $GaCl_3$-Mediated "Inverted" Formal [3 + 2]-Cycloaddition of Donor−Acceptor Cyclopropanes to Allylic Systems. *J. Org. Chem.* **2018**, *83*, 8193. (b) Zotova, M. A.; Novikov, R. A.; Volodin, A. D.; Korlyukov, A. A.; Tkachev, Y. V.; Korolev, V. A.; Tomilov, Y. V. Four-Membered Cycle Formation Challenge: $GaCl_3$-Promoted Formal [2+2]-Cycloaddition of Donor−Acceptor Cyclopropanes to Bicyclobutylidene. *Eur. J. Org. Chem.* **2019**, 4207−4214.

(13) (a) Borisov, D. D.; Novikov, R. A.; Tomilov, Y. V. $GaCl_3$-Mediated Reactions of Donor−Acceptor Cyclopropanes with Aromatic Aldehydes. *Angew. Chem., Int. Ed.* **2016**, *55*, 12233. (b) Borisov, D. D.; Novikov, R. A.; Eltysheva, A. S.; Tkachev, Y. V.; Tomilov, Y. V. Styrylmalonates as an Alternative to Donor−Acceptor Cyclopropanes in the Reactions with Aldehydes: A Route to 5, 6-Dihydropyran-2-ones. *Org. Lett.* **2017**, *19*, 3731.

(14) (a) Novikov, R. A.; Denisov, D. A.; Potapov, K. V.; Tkachev, Y. V.; Shulishov, E. V.; Tomilov, Y. V. Ionic Ga-Complexes of Alkylidene- and Arylmethylidenemalonates and Their Reactions with Acetylenes: An In-Depth Look into the Mechanism of the Occurring Gallium Chemistry. *J. Am. Chem. Soc.* **2018**, *140*, 14381−14390. (b) Denisov, D. A.; Borisov, D. D.; Korolev, V. A.; Novikov, R. A.; Tomilov, Y. V. Three-Component $GaHal_3$-Promoted Reactions of Substituted Methylidenemalonates and Donor−Acceptor Cyclopropanes with Propargyl Halides: Cascade Diastereoselective Construction of Five-Membered Lactones. *J. Org. Chem.* **2019**, *84*, 6174−6182.

(15) Denisov, D. A.; Novikov, R. A.; Potapov, K. V.; Korolev, V. A.; Shulishov, E. V.; Tomilov, Y. V. 1,1'-Bicyclopropyl-2,2-Dicarboxylate and Cyclopropylmethylidenemalonate as Homovinylogs and Vinylogs of Donor-Acceptor Cyclopropanes. *ChemistrySelect* **2016**, *1*, 6374−6381.

(16) Denisov, D. A.; Borisov, D. D.; Potapov, K. V.; Novikov, R. A.; Tomilov, Y. V. 4-Phenylspiro[2.2]Pentane-1,1-Dicarboxylate: Synthesis and Reactions with $EtAlCl_2$ and 4,5-Diazaspiro[2.4]Hept-4-Ene Derivative. *Mendeleev Commun.* **2019**, *29*, 417−418.

(17) Kreft, A.; Jones, P. G.; Werz, D. B. The Cyclopropyl Group as a Neglected Donor in Donor−Acceptor Cyclopropane Chemistry. *Org. Lett.* **2018**, *20*, 2059−2062.

(18) Korotkov, V. S.; Larionov, O. V.; Hofmeister, A.; Magull, J.; De Meijere, A. $GaCl_3$-Catalyzed Insertion of Diazene Derivatives into the Cyclopropane Ring. *J. Org. Chem.* **2007**, *72*, 7504−7510.

(19) Wu, J.; Winiarz, P.; Patel, D.; de Jong, J.; Tong, D.; Chidley, T.; Vemula, N.; Pagenkopf, B. L. Synthesis of Hexahydropyridazines by [4 + 2] Cycloaddition of Donor−Acceptor Cyclobutanes and cis-Diazenes. *Org. Lett.* **2020**, *22*, 3140−3144.

(20) (a) Mäki-Opas, I.; Hämäläinen, M.; Moilanen, L. J.; Haavikko, R.; Ahonen, T. J.; Alakurtti, S.; Moreira, V. M.; Muraki, K.; Yli-Kauhaluoma, J.; Moilanen, E. Pyrazine-Fused Triterpenoids Block the TRPA1 Ion Channel in Vitro and Inhibit TRPA1-Mediated Acute Inflammation in Vivo. *ACS Chem. Neurosci.* **2019**, *10*, 2848−2857. (b) Xin, X.; Zimmermann, S.; Flegel, J.; Otte, F.; Knauer, L.; Strohmann, C.; Ziegler, S.; Kumar, K. Unravelling the Synthesis and Chemistry of Stable, Acyclic, and Double-Deficient 1,3-Butadienes: An Endo-Selective Diels−Alder Route to Hedgehog Pathway Inhibitors. *Chem.—Eur. J.* **2019**, *25*, 2717−2722. (c) Cho, W.; Koo, J. Y.; Park, Y.; Oh, K.; Lee, S.; Song, J.-S.; Bae, M. A.; Lim, D.; Lee,

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX

D.-S.; Park, S. B. Treatment of Sepsis Pathogenesis with High Mobility Group Box Protein 1-Regulating Anti-Inflammatory Agents. *J. Med. Chem.* **2017**, *60*, 170−179. (d) Laavola, M.; Haavikko, R.; Hämäläinen, M.; Leppänen, T.; Nieminen, R.; Alakurtti, S.; Moreira, V. M.; Yli-Kauhaluoma, J.; Moilanen, E. Betulin Derivatives Effectively Suppress Inflammation in Vitro and in Vivo. *J. Nat. Prod.* **2016**, *79*, 274−280.

(21) (a) Lee, S.; Nam, Y.; Koo, J. Y.; Lim, D.; Park, J.; Ock, J.; Kim, J.; Suk, K.; Park, S. B. A Small Molecule Binding HMGB1 and HMGB2 Inhibits Microglia-Mediated Neuroinflammation. *Nat. Chem. Biol.* **2014**, *10*, 1055−1060. (b) Fejes, Z.; Mándi, A.; Komáromi, I.; Majoros, L.; Batta, G.; Herczegh, P. A Synthetic and in Silico Study on the Highly Regioselective Diels-Alder Reaction of the Polyenic Antifungal Antibiotics Natamycin and Flavofungin. *Tetrahedron Lett.* **2010**, *51*, 4968−4971. (c) Grange, R. L.; Gallen, M. J.; Schill, H.; Johns, J. P.; Dong, L.; Parsons, P. G.; Reddell, P. W.; Gordon, V. A.; Bernhardt, P. V.; Williams, C. M. [4+2] Cycloaddition Reactions between 1,8-Disubstituted Cyclooctatetraenes and Diazo Dienophiles: Stereoelectronic Effects, Anticancer Properties and Application to the Synthesis of 7,8-Substituted Bicyclo [4.2.0] Octa-2,4-Dienes. *Chem.—Eur. J.* **2010**, *16*, 8894−8903. (d) Brummond, K. M.; Mao, S.; Shinde, S. N.; Johnston, P. J.; Day, B. W. Design and Synthesis of a Library of Tetracyclic Hydroazulenoisoindoles. *J. Comb. Chem.* **2009**, *11*, 486−494. (e) Li, J. J.; Chao, H.-G.; Wang, H.; Tino, J. A.; Lawrence, R. M.; Ewing, W. R.; Ma, Z.; Yan, M.; Slusarchyk, D.; Seethala, R.; et al. Discovery of a Potent and Novel Motilin Agonist. *J. Med. Chem.* **2004**, *47*, 1704−1708.

(22) Cornelis, S.; Kersse, K.; Festjens, N.; Lamkanfi, M.; Vandenabeele, P. Inflammatory Caspases: Targets for Novel Therapies. *Curr. Pharm. Des.* **2007**, *13*, 367−385.

(23) Rudawska, K.; Ptasiewicz-Bąk, H. The Crystal Structures of Tetra-n-Butylammonium Salts of $GaCl^-_4$, $GaBr^-_4$ and GaI^-_4. *J. Coord. Chem.* **2003**, *56*, 1567−1574.

(24) Novikov, R. A.; Borisov, D. D.; Tarasova, A. V.; Tkachev, Y. V.; Tomilov, Y. V. Three-Component Gallium(III)-Promoted Addition of Halide Anions and Acetylenes to Donor−Acceptor Cyclopropanes. *Angew. Chem., Int. Ed.* **2018**, *57*, 10293−10298.

(25) Alberti, M. N.; Orfanopoulos, M. Concerning the Reactivity of PTAD with Isomeric Dienes: The Mechanism of the Diels−Alder Cycloaddition. *Org. Lett.* **2009**, *11*, 1659−1662.

(26) Chidley, T.; Vemula, N.; Carson, C. A.; Kerr, M. A.; Pagenkopf, B. L. Cascade Reaction of Donor−Acceptor Cyclopropanes: Mechanistic Studies on Cycloadditions with Nitrosoarenes and cis-Diazenes. *Org. Lett.* **2016**, *18*, 2922−2925.

(27) (a) Narangoda, C. J.; Lex, T. R.; Moore, M. A.; McMillen, C. D.; Kitaygorodskiy, A.; Jackson, J. E.; Whitehead, D. C. Accessing the Rare Diazacyclobutene Motif. *Org. Lett.* **2018**, *20*, 8009−8013. (b) Scott, L. T.; Erden, I.; Brunsvold, W. R.; Schultz, T. H.; Houk, K. N.; Paddon-Row, M. N. Competitive [6 + 2], [4 + 2], and [2 + 2] Cycloadditions. Experimental Classification of Two-Electron Cycloaddends. *J. Am. Chem. Soc.* **1982**, *104*, 3659−3664.

(28) Goncharova, I. K.; Silaeva, K. P.; Arzumanyan, A. V.; Anisimov, A. A.; Milenin, S. A.; Novikov, R. A.; Solyev, P. N.; Tkachev, Y. V.; Volodin, A. D.; Korlyukov, A. A.; Muzafarov, A. M. Aerobic Co-/N-Hydroxysuccinimide-Catalyzed Oxidation of p-Tolylsiloxanes to p-Carboxyphenylsiloxanes: Synthesis of Functionalized Siloxanes as Promising Building Blocks for Siloxane-Based Materials. *J. Am. Chem. Soc.* **2019**, *141*, 2143−2151.

(29) Tsedilin, A. M.; Fakhrutdinov, A. N.; Eremin, D. B.; Zalesskiy, S. S.; Chizhov, A. O.; Kolotyrkina, N. G.; Ananikov, V. P. How sensitive and accurate are routine NMR and MS measurements? *Mendeleev Commun.* **2015**, *25*, 454−456.

(30) (a) Corey, E. J.; Chaykovsky, M. Dimethyloxosulfonium Methylide ($(CH_3)_2SOCH_2$) and Dimethylsulfonium Methylide ($(CH_3)_2SCH_2$). Formation and Application to Organic Synthesis. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364. (b) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. Scope and Mechanism for Lewis Acid-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes: Evidence for a Stereospecific Intimate Ion Pair Pathway. *J. Am. Chem. Soc.* **2008**, *130*, 8642−8650.

(31) Perkowski, A. J.; You, W.; Nicewicz, D. A. Visible Light Photoinitiated Metal-Free Living Cationic Polymerization of 4-Methoxystyrene. *J. Am. Chem. Soc.* **2015**, *137*, 7580−7583.

(32) Wang, C.; Gong, S.; Liang, Z.; Sun, Y.; Cheng, R.; Yang, B.; Liu, Y.; Yang, J.; Sun, F. Ligand-Promoted Iridium-Catalyzed Transfer Hydrogenation of Terminal Alkynes with Ethanol and Its Application. *ACS Omega* **2019**, *4*, 16045−16051.

(33) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. Transition-Metal-Catalyzed Reactions of Diazo Compounds. 1. Cyclopropanation of Double Bonds. *J. Org. Chem.* **1980**, *45*, 695−702.

(34) Higgins, M. A.; Marcin, L. R.; Christopher Zusi, F.; Gentles, R.; Ding, M.; Pearce, B. C.; Easton, A.; Kostich, W. A.; Seager, M. A.; Bourin, C.; et al. Triazolopyridine Ethers as Potent, Orally Active MGlu2 Positive Allosteric Modulators for Treating Schizophrenia. *Bioorg. Med. Chem.* **2017**, *25*, 496−513.

(35) Kallemeyn, J.; Mulhern, M.; Ku, Y.-Y. Asymmetric Synthesis of Di- and Trisubstituted Cyclopropanes through an Intramolecular Ring Closure. *Synlett* **2011**, 535−538.

(36) Melancon, B. J.; Perl, N. R.; Taylor, R. E. Competitive Cationic Pathways and the Asymmetric Synthesis of Aryl-Substituted Cyclopropanes. *Org. Lett.* **2007**, *9*, 1425−1428.

(37) Chanthamath, S.; Phomkeona, K.; Shibatomi, K.; Iwasa, S. Highly Stereoselective Ru(II)−Pheox Catalyzed Asymmetric Cyclopropanation of Terminal Olefins with Succinimidyl Diazoacetate. *Chem. Commun.* **2012**, *48*, 7750.

(38) Bobileva, O.; Bokaldere, R.; Gailite, V.; Kaula, I.; Ikaunieks, M.; Duburs, G.; Petrovska, R.; Mandrika, I.; Klovins, J.; Loza, E. Synthesis and Evaluation of (E)-2-(Acrylamido)Cyclohex-1-Enecarboxylic Acid Derivatives as HCA1, HCA2, and HCA3 Receptor Agonists. *Bioorg. Med. Chem.* **2014**, *22*, 3654−3669.

(39) Singh, P.; Kaur, N.; Banerjee, P. Regioselective Brønsted Acid-Catalyzed Annulation of Cyclopropane Aldehydes with N′-Aryl Anthranil Hydrazides: Domino Construction of Tetrahydropyrrolo-[1,2-a]Quinazolin-5(1H)Ones. *J. Org. Chem.* **2020**, *85*, 3393−3406.

https://dx.doi.org/10.1021/acs.joc.0c02293
J. Org. Chem. XXXX, XXX, XXX−XXX