# Photocatalyzed $[2 \sigma+2 \sigma]$ and $[2 \sigma+2 \pi]$ cycloadditions for the synthesis of bicyclo[3.1.1]heptanes and 5- or 6-membered carbocycles 

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#### Abstract

We report the use of photocatalysis for the homolytic ring-opening of carbonyl cyclopropanes. In contrast to previous studies, our approach does not require a metal co-catalyst or a strong reductant. The carbonyl cyclopropanes can be employed for both $[2 \sigma+2 \sigma]$ and $[2 \sigma+2 \pi]$ annulation with either alkenes/alkynes or bicyclo[1.1.0]butanes yielding cyclo-pent-anes/-enes and bicyclo[3.1.1]heptanes (BCHs) respectively. BCHs are promising bioisosteres for meta-substituted aromatic rings. Mechanistic studies, including DFT computation and a trapping experiment with DMPO, support a 1,3-biradical generated from the cyclopropane as a key intermediate for these transformations.




Radical chemistry has witnessed a renewal during the past few decades thanks to new mild methods to generate radicals, in particular through photocatalysis. ${ }^{1}$ Photochemistry enables the generation of radical species under mild conditions without the need of classical toxic or expensive radical precursors such as organotin reagents or samarium. Apart from single carbon radicals, which have been intensively studied, the reactivity of 1,2 biradicals has recently been the focus of strong interest, especially in the context of the excitation of conjugated $\pi$-carbonyl systems through energy transfer catalysis (Scheme 1A). . ${ }^{2,3}$ In contrast, the generation of non-conjugated 1,n biradicals through the homolytic cleavage of C-C bonds in carbocycles remains challenging due to the larger bond dissociation energy of a $\sigma \mathrm{C}-\mathrm{C}$ bond compared to a $\pi$ bond. The $1, n$ biradicals can then be applied in further cyclizations or ring expansions to rapidly increase the complexity of small molecules. ${ }^{4}$
In order to cleave a C-C bond in a homolytic fashion, a successful strategy is based on ring-opening reactions from highly strained cyclic structures. In 2022, Brown reported an energy transfer catalysis approach to promote such a transformation in the case of bicyclo[1.1.0]butanes (BCBs) bearing a naphthyl ketone substituent (Scheme 1A). ${ }^{\text {b }}$ Brown proposed that the reaction was proceeding via the generation of a cyclobutyl 1,3 biradical intermediate formed after excitation and homolytic fission of the C-C bond. They showed that the naphthyl group was crucial for
the success of the reaction. Compared to bicyclo[1.1.0]butanes, cyclopropanes are more common and easily accessible precursors for C-C bond cleavage. ${ }^{5}$ However, there is a large difference of ring strain between BCBs and cyclopropanes ( $66.3 \mathrm{Kcal} / \mathrm{mol}$ vs $29.0 \mathrm{Kcal} / \mathrm{mol}$ ), ${ }^{5 b}$ making the homolysis process less thermodynamically downhill for the latter.
Therefore, most efforts have focused on heterolytic cleavage of the $\mathrm{C}-\mathrm{C}$ bond to generate formal 1,3 dipole equivalents. ${ }^{5 a}$ However, to enhance the reactivity of cyclopropanes, donor-acceptor systems are usually required along with addition of a Lewis acid. A single carbonyl group as acceptor is usually not sufficient to promote heterolytic ring opening, except under very harsh conditions (Scheme 1B, path a). ${ }^{5 d}$ A different activation approach is therefore required for this type of substrates. This was recently achieved through one electron reduction of the carbonyl group to a radical anion, leading to immediate ring opening (Scheme 1B, path b). ${ }^{6-10}$ Due to the high redox potential of most carbonyl-substituted cyclopropanes, ${ }^{6 \mathrm{~b}}$ strong reductants were required such as $\mathrm{Sm},{ }^{6 \mathrm{a}, \mathrm{c}}$ the combination of Ti and $\mathrm{Mn}^{7}$ or more recently boron and pyridine derivatives. ${ }^{8}$ Photoredox catalysis could be also applied, yet the coordination with a Lewis acidic transition metal is crucial to facilitate the reduction as reported by Yoon ${ }^{9}$ and Meggers. ${ }^{10}$


Scheme 1. A. Homolytic cleavage of C-C bonds. B. Activation of carbonyl cyclopropanes. C. Our work. D. BCH as bioisosteres. PA: diphenyl hydrogen phosphate. TX : thioxanthone.

In contrast, energy transfer catalysis has been only rarely used to activate carbonyl cyclopropanes (Scheme 1B, path c). Applications are limited to the epimerization of stereocenters ${ }^{11}$ or intramolecular rearrangements, ${ }^{12}$ probably due to the fast recombination rate of the biradical. ${ }^{11-13}$ To the best of our knowledge, energy-transfer catalysis has never been exploited to promote intermolecular annulation reactions of cyclopropanes with $\pi$ or $\sigma$ bonds as partners. Herein, we report the light activation of carbonyl substituted cyclopropanes for cycloaddition with alkyne, olefins and bicyclo[1.1.0]butanes (BCBs) in absence of any reducing or metal coordinating agent (Scheme 1C), giving rise to the synthesis of 5 and 6-membered carbocycles, as well as bicyclo $3,1,1$ ]heptane ( BCH ) derivatives.
BCHs have been recently investigated as bioisosteres for meta-substituted arenes ${ }^{14,15}$ as part of a resurging interest in non-aromatic benzene bioisosteres (Scheme 1D). ${ }^{16}$ The synthesis of BCHs is however challenging. Most recent studies focus on functionalizing [3.1.1]propellane as a preformed skeleton of BCHs. ${ }^{14,15}$ However, the poor stability of [3.1.1]propellane along with difficult handling and storage still limit applications. In contrast, bicyclo[1.1.0]butane derivatives are stable at room temperature and easy to handle. The synthesis of BCBs is now well developed due to the re-
cent focus of interest in their use as building blocks, especially in photocatalytic processes. ${ }^{17}$ During completion of this project, ${ }^{18}$ the first annulations of cyclopropanes and BCBs to give highly functionalized BCHs were reported by Molander and Li via oxidative and reductive electron transfer processes, respectively. ${ }^{19}$ Interestingly, these works are highly complementary to our approach from the mode of activation point of view (redox activation vs homolytic cleavage). In addition, X -Ray analysis of the structure of the obtained highly substituted BCHs demonstrated their potential as bioisosteres for 1,2,4,5 tetra-substituted benzene derivatives, which are of high relevance for the pharmaceutical industry. ${ }^{16 \mathrm{~d}}$

We started our investigation with phenylcarbonyl cyclopropane 1a with two methyl groups on the ring as a model substrate as the presence of the dimethyl group has led to enhanced reactivity in previous studies (Table 1). ${ }^{6,7}$ To enhance the synthetic value of our work, we chose phenyl acetylene (3a) as a radical trap under visible light irradiation, as it has been only rarely successful in $[2 \sigma+2 \pi]$ cycloadditions ${ }^{6}$ when compared to olefin partners. ${ }^{6-10}$ Based on the previous study of Brown and co-workers on car-bonyl-substituted BCBs, ${ }^{4 b}$ thioxanthone-based catalysts (PC1 and PC2) were chosen as energy transfer catalysts for the reaction. No cycloaddition product formed with PC1
(entry 1), but gratifyingly $42 \%$ of 2a was obtained with PC2 (entry 2). In both cases, good conversion was observed but the major product formed was ether $\mathbf{2 a 1}$ (83\% and 50\% yield for entries 1 and 2 respectively). This background reaction was likely due to competitive oxidation of the radical intermediate at the tertiary carbon. We also examined acri-dinium-based photocatalyst PC3 (entry 3). However, only little conversion of 1a was obtained. Carbazole-based photocatalyst PC4 failed to give any product and the starting material was recovered (entry 4). In contrast, the iridiumbased photocatalyst PC5 gave 2a in 77\% NMR yield (entry 5). A lower yield was obtained in other solvents (see SI for
further details). An attempt to reduce the amount of trapping reagent to 2 equivalents resulted in a drop of the yield to $52 \%$ (entry 6) due to the competition with intramolecular cyclization to give 2a2. This phenomenon was described in a previous report by Procter and co-workers. ${ }^{6 c}$ In order to reduce the amount of phenyl acetylene (3a) used, we chose substrate 1b bearing diester groups to inhibit the oxidation reaction occurring at the tertiary carbon. In fact, the stoichiometry of phenylacetylene (3a) could be successfully diminished to only 1.5 equivalents to give $79 \%$ of product 2b (entries 7-10).

Table 1. Optimization of reaction condition.


| Entry | Photocatalyst | Concentration | $\mathbf{R}$ | x equiv. | Yield of 2 (\%) ${ }^{\text {a }}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | PC1 (10 mol\%) | 0.2 M | Me | 5 | $0^{\mathrm{b}}$ |
| 2 | PC2 (10 mol\%) | 0.2 M | Me | 5 | $42^{\mathrm{b}}$ |
| 3 | PC3 (10 mol\%) | 0.2 M | Me | 5 | 14 |
| 4 | PC4 (10 mol\%) | 0.2 M | Me | 5 | 0 |
| 5 | PC5 (1 mol\%) | 0.2 M | Me | 5 | $77(74)$ |
| 6 | PC5 (1 mol\%) | 0.2 M | Me | 2 | 52 |
| 7 | PC5 (1 mol\%) | 0.2 M | $\mathrm{CO}_{2} \mathrm{Me}$ | 5 | 69 |
| 8 | PC5 (1 mol\%) | 0.1 M | $\mathrm{CO}_{2} \mathrm{Me}$ | 5 | 73 |
| 9 | PC5 (1 mol\%) | 0.1 M | $\mathrm{CO}_{2} \mathrm{Me}$ | 2 | 72 |
| 10 | PC5 (1 mol\%) | 0.1 M | $\mathrm{CO}_{2} \mathrm{Me}$ | 1.5 | $79(78)$ |

Reaction conditions: 0.1 mmol 1 ( 1 equiv.), one Kessil lamp ( $440 \mathrm{~nm}, 40 \mathrm{~W}$ ). a ${ }^{1} \mathrm{H}$ NMR yields were determined with $\mathrm{CH}_{2} \mathrm{Br}_{2}$ as an internal standard. Isolated yield after chromatography is given in brackets. bUsing a 427 nm lamp to better fit the absorption spectra of the catalysts, full conversion of $\mathbf{1 a}$ and $\mathbf{2 a 1}$ as main product.

With the optimized conditions in hands, we investigated the scope of the $[2 \sigma+2 \pi]$ cycloaddition of phenylacetylene (3a) with different cyclopropanes (Scheme 2A). Carbonyl cyclopropanes bearing different vicinal di-substituents such as methyl, ester or fluorine groups are suitable substrates, giving products 2a-2d in 53-78\% yield. Starting from a substrate bearing a methyl group at the ortho aryl position resulted in a lower yield of $45 \%$ (product 2e). Ortho-substituents can affect the conjugation between carbonyl groups and aromatic systems, ${ }^{6 c}$ leading to a destabilized biradical intermediate. An electron donating methoxy group on the phenyl ring delivered product $\mathbf{2 f}$ with a lower yield than
substrate $\mathbf{1 g}$ and $\mathbf{1 h}$ with an electron withdrawing group ( $\mathrm{CF}_{3}, \mathrm{~F}$ ). Mono-substituted cyclopropanes could also be used in this transformation but led to lower yields (products $\mathbf{2 i - k}$ ). The reaction could also be applied to synthesize spiro[4.3] octene and spiro[4.5]decene products $\mathbf{2 l}$ and $\mathbf{2 m}$ from the corresponding cyclopropanes. With naphthalene as aromatic moiety, product 2 n was obtained in $68 \%$ yield. We did not observe the formation of dearomatized products in contrast to previous reports on the dearomative cyclization of naphthyl alkyl ketones and olefins. ${ }^{20,21}$ We speculate that the dimethyl-substituent on the cyclopropane would stabilize the biradical intermediate, favoring the ring-opening pathway over the cyclization on the naphthyl ring.


Scheme 2. Substrate scope. Reaction conditions: a 1 (1 equiv.), 3 (5 equiv.), MeOH ( 0.1 M ), 1 Kessil lamp ( $440 \mathrm{~nm}, 40 \mathrm{~W}$ ), 16 h . b Same as method ${ }^{\text {a }}$ with 3 or 5 ( 1.5 equiv.).c Same as method ${ }^{\text {b }}$ in $\mathrm{CH}_{3} \mathrm{CN}$ ( 0.1 M ). d 1 ( 1 equiv.), 3 or 5 or 11 ( 2.5 equiv.) $30 \mathrm{~mol} \%$ of $(\mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}, \mathrm{CH}_{3} \mathrm{CN}(1 \mathrm{~mL})$. e. with $30 \mathrm{~mol} \%$ of $(\mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}, \mathrm{CH}_{3} \mathrm{CN}(1 \mathrm{~mL})$. f. Same as ${ }^{\text {a }}$ with $30 \mathrm{~mol} \%$ of $(\mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}$. See SI for experimental details. dr was determined from the crude NMR. brsm: based on recovered starting material.

We then investigated the scope of alkyne partners. 5 equivalents of alkyne were required with dimethyl-substituted cyclopropane 1a (products $\mathbf{2 o - q}$ ), but only 1.5 or 2.5 equivalents were enough with cyclopropane $\mathbf{1 b}$ having a diester group (products $2 \mathbf{r}-\mathbf{x}$ ), and higher yields were obtained. The reaction was successful with both electron-donating and electron-withdrawing substituents on the arene (products 2o-u). Heterocyclic alkyne $\mathbf{3 g}$ and carbonyl-substituted alkynes $\mathbf{3 h}$ and $\mathbf{3 i}$ were also successfully employed to deliver cyclopentene $\mathbf{2 v}, \mathbf{2 w}, \mathbf{2 x}$ in $81 \%, 37 \%$ and $44 \%$ respectively. With an internal alkyne, only $20 \%$ of product was observed in the NMR of the crude mixture after 48 hours of reaction time. Unfortunately, there is no product observed with non-activated aliphatic alkynes (see SI).
We then studied the generality of the protocol for more established olefins as partners (Scheme 2B). The products 4 a and $\mathbf{4 b}$ of cycloaddition with styrene were obtained for both substrate 1a and 1b in excellent yields ( $82 \%$ and $90 \%$ respectively). Product 4c, 4d bearing electron donating and withdrawing group were obtained in $84 \%$ and $55 \%$ respectively. The cis-diastereomer was isolated as the major product, which contrasts with what had been observed in the previous studies by Lin and Yoon. ${ }^{7,9}$. The reaction becomes sluggish when it comes to mono-substituted cyclopropanes and $30 \mathrm{~mol} \%$ of diphenyl hydrogen phosphate (PA) as cocatalyst and a longer reaction time were required, leading to product $\mathbf{4 e} \mathbf{- 4 g}$ in 54-89\% yield and moderate dr using 1,1-diphenyl ethylene as coupling partner. Only $22 \%$ of product $4 h$ was observed starting from non-substituted cyclopropyl phenyl ketone. We then investigated the scope of olefin partners with cyclopropane 1b. With 1,1-diphenyl ethylene, we isolated product $4 \mathbf{i}$ in $84 \%$ yield. Carbonyl substituted olefins were also compatible as coupling partners, but required the use of $30 \mathrm{~mol} \%$ of PA to accelerate the reaction, resulting in product $\mathbf{4 j}$ and $\mathbf{4 k}$ in $77 \%$ and $58 \%$ yield, respectively. The same conditions were used for a silyl and a dialkyl substituted olefin, giving products $\mathbf{4 l}$ and $\mathbf{4 m}$ in $43 \%$ and $69 \%$ yield. When a diene was used as a coupling partner, only $(3+2)$ annulation was observed and cyclopentane $\mathbf{4 n}$ was isolated in $71 \%$ yield. Enamides were also good coupling partners for the reaction, even without addition of the PA co-catalyst: N-Vinylpyrrolidinone and N -vinylphthalimide, yielded product $\mathbf{4 o}$ and $\mathbf{4 p}$ in $83 \%$ and $55 \%$ yield. Heteroaromatic olefins are also compatible with the reaction conditions, but led to lower yields: Products $\mathbf{4 q}$ and $4 \mathbf{r}$ were obtained in $49 \%$ and $26 \%$ yield. The lower yield can be rationalized by a fast polymerization of these substrates. A pyridine substituted olefin only gave trace of products (see SI).
Intramolecular annulation was also possible with both substrates bearing either an alkyne or an olefin ( $\mathbf{6 a}$ and $\mathbf{6 b}$ ), yielding $46 \%$ of product $7 \mathbf{a}$ and $67 \%$ of product $7 \mathbf{b}$ (Scheme 2 C ). The scope was further extended to cyclobutane $\mathbf{8}$ as strained ring (Scheme 2D). To our delight, cyclohexene 9a, 9b were isolated in $57 \%$ and $49 \%$, respectively.
To demonstrate the synthetic versatility of the products, we removed the aryl ketone required for reactivity (Scheme 3). A Baeyer-Villiger reaction on cis-4d did not proceed to completion and we observed that only the minor trans-4d had reacted. Under acidic conditions, it was possible to convert
the diastereoisomers mixture of $\mathbf{4 d}$ to only the trans isomer. After Baeyer-Villiger reaction ${ }^{9 b}$ and saponification, product 4da was obtained in 55\% yield over 3 steps.


## Scheme 3. Removal of the aryl ketone on 4d.

We then investigated BCBs 11 as $2 \sigma$ partners for cyclization with cyclopropane 1b (Scheme 2E). We were delighted to observe the formation of BCH 10a in 72\% yield in the presence of diphenyl hydrogen phosphate (PA) as co-catalyst using phenyl-methylester substituted BCB 11a as partner. Cyclopropane 1a, in contrast, gave only trace amount of the desired product although full conversion of 1a was observed. Other control experiments show that there was only trace of product observed in the absence of PA or a photocatalyst. (See SI for optimization details). The reaction is compatible with both electron-donating and electron-withdrawing groups on the carbonyl arene ring (products 10bd). A mono-ester substituted cyclopropane gave product 10e in moderate yield (42\%). In parallel, we observed that $o$-fluoroaryl substituted BCB 11b gave better yield (10f, $84 \%$ vs $10 a, 72 \%)$. We then further developed the scope with BCB 11b. $p$-Phenyl substituted cyclopropane 1t delivered product $\mathbf{1 0 g}$ in $\mathbf{7 4} \%$ yield. However, dibenzofuran cyclopropane $\mathbf{1 0}$ gave only $24 \%$ of product $\mathbf{1 0 h}$. Replacing one ester group by a chlorine or a fluorine resulted in a mixture of diastereoisomers in moderate yield, yet good diastereoselectivity (products 10i, 42\% yield, dr $91: 9$ and 10j with $51 \%$ yield and dr 81:19). An estrone substituted cyclopropane gave 10k in $21 \%$ yield. In this case, an excellent diastereomeric ratio was observed, probably due to the high steric hindrance of the estrone group. BCBs 11 with other aryl and ester substituents were then studied. A chlorinated BCB gave product $\mathbf{1 0 1}$ in 93\% yield. The reaction tolerated also other functional groups such as $\mathrm{CF}_{3}$, an ester and $\mathrm{OCF}_{3}$, giving products $\mathbf{1 0 m} \mathbf{- 1 0 o}$ in $55-70 \%$ yield. A methoxy group led to $30 \%$ of product $\mathbf{1 0 p}$ and $41 \%$ of starting material 1b was recovered. In most cases, full conversion of the BCB 11 was observed due to background reactions such as polymerization or the formation of cyclobutenes. A methyl group was better tolerated and gave $\mathbf{1 0 q}$ in $\mathbf{7 5 \%}$ yield. The reaction with a BCB bearing an allyl ester delivered product 10r in $52 \%$ yield. There was no $[2 \sigma+2 \pi]$ cycloaddition observed with this substrate, indicating that the C-C $\sigma$ bond on BCB is more reactive than inactivated C-C $\pi$ bonds. A benzyl ester was also well tolerated (BCH 10s).
To investigate further modification of the BCH scaffold, we performed the saponification of ester 10i, yielding carboxylic acid 12 in almost quantitative yield (Scheme 4A). The reaction happened selectively on the ester group next to the chlorine atom. Esterification of acid $\mathbf{1 2}$ with either estrone or Ezetimibe, a cholesterol-lowering drug, gave esters 13 and 14 in $49 \%$ and $84 \%$ yield respectively (Eq. 1 and 2). Weinreb amide 15 was also synthesized in $79 \%$ yield from carboxylic acid 12 (Eq. 3). Selective amidation of the ester group of $\mathbf{1 2}$ was performed following a reported protocol, ${ }^{22}$
delivering amide 16 in 67\% yield (Eq. 4). A scale-up experiment was also performed and $70 \%$ of $\mathbf{1 0 l}$ was isolated on a 1 mmol scale (Eq.5). CBS reduction of ketone 101 gave alcohol 17 in $42 \%$ yield with 95:5 diastereoselectivity (Eq. 6) for the cis diastereomer. Ketone $\mathbf{1 0 1}$ was then treated with hydrazine 18, delivering 71\% of hydrazone 19a for X-ray analysis (CCDC number 223800) (Eq. 7).
For the design of benzene bioisosteres, it is essential that: 1) the linker is rigid, so that the substituents can be fixed conformationally in space; 2) the distances between substituents must be as close as possible to those in substituted benzene derivatives. ${ }^{16 \mathrm{a}-\mathrm{c}}$ To assess these parameters, we analyzed the $\mathrm{d}_{1}, \mathrm{~d}_{2}, \mathrm{~d}_{3}$, and $\mathrm{r}_{1}, \mathrm{r}_{2}, \mathrm{r}_{3}$ values from the X-ray data of 19a and compared them with those of 1,2; 1,3 and 1,4 substituted benzenes from the literature ${ }^{16}$ (Scheme 4B).

The values obtained from the X-ray data of 19a were indeed close to those reported for substituted benzenes and known bioisosteres. ${ }^{16 \mathrm{a}, \mathrm{c}, \mathrm{h}, \mathrm{i}}$ For a more precise comparison, we performed DFT calculation on compound 19b, the benzene derivative with the exact same substituents as 19a. The calculated distances are close to those obtained from the X-Ray data of 19a, supporting the potential of BCH scaffolds as bioisosteres of $1,2,4,5$ tetra-substituted benzenes. This benzenoid moiety is encountered in the core of several small molecular drugs. ${ }^{16 c}$ However, although the substituents in the "meta" position of $\mathbf{1 9 a}$ are in a plane with a dihedral angle of $0.6^{\circ}$, this is not the case for the "ortho" and "para" substituents. Nevertheless, bioisosteres have been demonstrated to be successful even if they do not mimic perfectly the planarity of the benzene ring. ${ }^{16 g}$

B. BCHs as potential bioisosteres for substituted benzenes
1,2,4,5 tetra-substituted


|  | Substituted <br> benzenes | $X^{\text {a,b }}$ distance from X-Ray of 19a <br> $\mathrm{a}, \mathrm{b}:$ position of carbon | distances calculated <br> for 19 b |
| :--- | :---: | :---: | :---: |
| $\mathrm{~d}_{1}$ | $4.9-5.0 \AA$ | $4.66^{4,6} \AA, 4.92^{1,9} \AA, 4.67^{1,8} \AA$ | $4.93^{4,6} \AA, 4.93^{1,8} \AA$ |
| $\mathrm{r}_{1}$ | $2.4-2.5 \AA$ | $2.15^{3,5} \AA, 2.58^{2,7} \AA$ | $2.44^{3,5} \AA, 2.44^{2,7} \AA$ |
| $\mathrm{~d}_{2}$ | $2.9-3.1 \AA$ | $2.90^{1,4} \AA, 3.08^{6,8} \AA, 3.28^{6.9} \AA$ | $2.98^{1,4} \AA, 3.07^{6,8} \AA$ |
| $\mathrm{r}_{2}$ | $1.4-1.5 \AA$ | $1.56^{2,3} \AA, 1.56^{7,5} \AA$ | $1.41^{2,3} \AA, 1.40^{7,5} \AA$ |
| $\mathrm{~d}_{3}$ | $5.7-5.8 \AA$ | $5.65^{6,1} \AA, 5.63^{4,8} \AA, 5.09^{4,9} \AA$ | $5.78^{6,1} \AA, 5.78^{4,8} \AA$ |
| $\mathrm{r}_{3}$ | $2.6-2.8 \AA$ | $2.80^{2,5} \AA, 2.84^{3,7} \AA$ | $2.81^{2,5} \AA, 2.82^{3,7} \AA$ |



Scheme 4. A. Modification of BCH products. B. BCHs as a potential bioisosteres for $\mathbf{1 , 2 , 4 , 5}$ tetra-substituted benzenes.

## A. Different mechanism alternatives for cyclopropane activation



## B. UV-VIS absorption



## C. Stern - Volmer quenching



## E. Direct excitation



1a or 1b


3a, 5 equiv

$8 \mathrm{~h}, \mathrm{rt}$


2a or 2b

| $R$ | 352 nm <br> (Rayonnet) | 390 nm <br> (Kessil Lamp) | 440 nm <br> (Kessil Lamp) |
| :---: | :---: | :---: | :---: |
| $\mathrm{Me}(\mathbf{2 a})$ | $8 \%$ | $57 \%$ | $0 \%$ |
| $\mathrm{CO}_{2} \mathrm{Me} \mathrm{(2b)}$ | $6 \%$ | $40 \%$ | $0 \%$ |

Scheme 5. Mechanistic investigation. A. Different mechanism alternative for cyclopropane activation. B. UV-Vis absorption spectra. C. Stern-Volmer quenching. D. Control experiments. E. Direct excitation.

In order to gain more information about the reaction mechanism, the quantum yield was first measured to be 0.4 . This result is consistent with a photocatalytic reaction or a radical chain proceeding with low efficiency. Assuming a photocatalytic process, three different mechanisms could be considered (Scheme 5A). i. Electron transfer from the activated catalyst for the generation of a radical anion IB after ring opening of ketyl radical anion IA, ii. Formation of an EDA complex IIA followed by single electron transfer and ring opening to give radical cation/anion pair IIB or iii. Energy transfer from the catalyst to generate 1,3 biradical IIIB from activated intermediate IIIA. Given the redox potentials of the [Ir] photocatalyst $\left(\mathrm{E}_{1 / 2}{ }^{\mathrm{PC}} / \mathrm{PC+}=-0.96 \mathrm{~V}\right.$ vs SCE; $\mathrm{E}_{1 / 2}{ }^{\mathrm{PC}} / \mathrm{PCC}-$ $=+0.66 \mathrm{~V}$ vs SCE$)^{23}$ in comparison to $\mathbf{1 b}\left(\mathrm{E}_{1 / 2}=-1.91 \mathrm{~V}\right.$ vs SCE), styrene $\left(\mathrm{E}_{1 / 2}=+1.97 \mathrm{~V}\right)^{23}$ and $\mathrm{BCBs}\left(\mathrm{E}_{1 / 2}=+1.54 \mathrm{~V}\right.$ vs SCE), ${ }^{17 \mathrm{~d}}$ a single electron transfer mechanism (pathway i) appears less probable. Based on previous studies, the formation of a ketyl radical via a proton-coupled electron transfer (PCET) process in the presence of PA still appears thermodynamically difficult in the absence of a stoichiometric reductant. ${ }^{24}$
As a photoredox/single electron transfer mechanism appeared not probable, we conducted NMR analysis, UV-VIS
absorption and Stern-Volmer quenching experiments to see if there was a formation of an EDA complex (pathway ii). Initially, we observed a shift in the chemical shift of aromatic signals on cyclopropanes 1a, 1b in the present of $\mathbf{3 a}$, $\mathbf{5 a}$, and $\mathbf{1 1 h}$ (see SI), suggesting intermolecular interactions. However, both UV-VIS absorption and Stern-Volmer quenching experiments indicated that there was no difference in photophysical properties between cyclopropane 1a and a mixture of 1a + 3a (Scheme 5B and 5C). Hence, the hypothesis of a light-excited EDA complex seems to be unlikely. Nevertheless, the Stern-Volmer experiments demonstrated that cyclopropane 1a is the species that quenched the emission signal of the photocatalyst. Indeed, under standard conditions in absence of alkyne 3a, cyclopropane 1b was transformed into ring-opening reduction product 1ba and cyclization product 1bb (Scheme 5D, Eq. 8), meaning that the ring-opening reaction can happen even in the absence of coupling partners. Kinetic studies reveal that the reaction was $1^{\text {st }}$ order in $\mathbf{1 b}$ and zero ${ }^{\text {th }}$ order in $\mathbf{3 a}$ (see SI). These experiments taken together suggested that formation of radical cation/anion pair II via an EDA complex is less probable, and photocatalyst-promoted ring-opening is the key rate limiting step for this transformation.

## A. Radical trapping experiments



1b


TEMPO, 5 equiv.
 Kessil lamp 440 nm
$48 \mathrm{~h}, \mathrm{rt}$


## 1b

PC5 (1 mol\%) Kessil lamp



1a



DMPO, 5 equiv.
$\xrightarrow[\mathrm{CH}_{3} \mathrm{CN}(0.1 \mathrm{M})]{\substack{\text { 3a (5 equiv.) } \\ \text { PC5 } 1 \mathrm{~mol} \%}}$
Kessil lamp 440 nm
$48 \mathrm{~h}, \mathrm{rt}$




DMPO

48 h , rt

1bc, 11\%
(11)
$13 \%$ (With $\left.30 \mathrm{~mol} \%(\mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}\right)$

1 be 2b Not observed
(nanochip-ESI) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{25} \mathrm{NNaO}_{2}{ }^{+} 310.1777$; Found 310.1767 (APCI) m/z: $[\mathrm{M}+\mathrm{H}]^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{26} \mathrm{NO}_{2}{ }^{+}$288.1958; Found 288.1962.


Scheme 6. A. Radical trapping experiments. B. DFT calculation: (1) TDDFT computed Jablonski diagram on the low-lying excited states of PC5. (2) DFT computed free energy profile for the reaction of $\mathbf{1 a}$ and phenylacetylene $\mathbf{3 a}$ to form 2a. (3) Triplet energy of investigated photocatalysts (PC), NMR yields of 2a and conversion of 1a. Computations at the M06/TZP//M06/def2-SVP level using the COSMO implicit solvent model for methanol (see SI for further details). ${ }^{a 1} \mathrm{H}$ NMR yields were determined with $\mathrm{CH}_{2} \mathrm{Br}_{2}$ as an internal standard. Conversion of $\mathbf{1 a}$ is given in brackets.

Therefore, an energy transfer mechanism (pathway iii) to form the triplet state of cyclopropanes IIIA appeared more probable. No conversion was observed when performing
the reaction under air (Scheme 5D, Eq. 9), which is in agreement with oxygen being a triplet state quencher. ${ }^{25}$

Brown and co-worker demonstrated that either energy transfer catalysis under visible light or direct excitation under UV light would generate a 1,3 biradical intermediate from a naphthyl carbonyl substituted BCB. ${ }^{4 b}$ We therefore conducted our reaction in the absence of a photocatalyst under UV light irradiation. Indeed, both products 2a and 2b were observed after 48 hours (Scheme 5D, Eq.10), which supported further the formation of biradical IIIB. In accordance with this result, the UV-Vis spectrum of cyclopropane 1a exhibits light absorption in the UV region (Scheme 5B)To further support the presence of a biradical intermediate, we turned to radical trapping experiments (Scheme 6A). When 5 equivalents of TEMPO were added, $11 \%$ of $\mathbf{1 b c}$ was isolated, indicating the potential formation of a radical at the $\alpha$ position of the carbonyl (Eq. 11). 13\% of product 1bc was observed when performing the reaction with PA as co-catalyst. This result makes both pathway $\mathbf{i}$ and $\mathbf{i i}$ involving an enolate intermediate less probable. In order to provide further evidence for a biradical intermediate, we then use DMPO ( 5,5 -dimethyl-1-pyrroline N -oxide), one of the most established spin trapping reagent (Eq. 12). ${ }^{25 a}$ Interestingly, a mixture of nitrones $\mathbf{1 b d}$ and $\mathbf{1 b e}$ was isolated in $49 \%$ yield (ratio $48: 52$ ) and $41 \%$ yield (ratio $45: 55$ ) either with or without addition of $\mathbf{3 a}$. We hypothesize that the reaction happened via a homolytic cleavage of cyclopropane $\mathbf{1 b}$ to give biradical $\mathbf{I}$, followed by a radical addition from either position 1 or 3 on DMPO. In contrast to what happens with a single radical, the formed biradicals II or III are not stable. We speculate that a hydrogen atom transfer to yield product 1bd or 1be could be possible, although other mechanisms such as a single electron transfer followed by a proton transfer could be also considered.
Different from our observation, Lin had reported that radical 1a1 was detected upon reductive activation of cyclopropane 1a when trapping with DMPO (Eq. 13). ${ }^{7 a}$ Under our reaction conditions, a different HRMS signal corresponding to intermediate 1 a 2 or 1 a 3 was observed instead (Eq. 14). This divergent behavior in trapping experiments with DMPO is a strong support for a different mechanism in the two transformations, with the formation of a biradical being more likely in our case, rather than an enolate radical anion as described under reductive conditions.
In some cases, the addition of PA was required to promote the reaction. IR experiments conducted with cyclopropane $\mathbf{1 b}$, phenyl acetylene ( $\mathbf{3 a}$ ) and BCB (11h) showed that the $\mathrm{C}=0$ stretching signal in $\mathbf{1 b}$ and BCB were both affected by the addition of PA (see SI). Therefore, the role of PA may be to activate either the carbonyl group on the cyclopropane or the one on the BCB. Yoon and co-workers have shown that coordination of Lewis and Brønsted acids to the carbonyl group can lower the triplet energy of aryl olefin ketones. ${ }^{3 a, d}$ Hydrogen bonding also has a significant impact on the formation of triplet 1,3 diradical intermediates, as reported by Bach. ${ }^{11}$ In experiments performed in the dark, we observed conversion of BCB to cyclobutene in presence of PA, supporting further an activation effect.

At this stage, we had significant experimental support for an energy transfer mechanism leading to the formation of a biradical. However, the reported triplet energy values for activated catalyst PC5 ( $49.2 \mathrm{Kcal} / \mathrm{mol})^{26}$ and a similar carbonyl cyclopropane ( $74.2 \mathrm{Kcal} / \mathrm{mol})^{13 \mathrm{a}}$ indicated that such a pathway would be thermodynamically improbable. Puzzled by this result, we performed (TD)DFT computations at the M06 ${ }^{27} / \mathrm{TZP}^{28 a} / / \mathrm{M} 06 /$ def2-SVP ${ }^{28 \mathrm{~b}}$ level with an implicit methanol solvent using the COSMO ${ }^{28 c}$ model (see SI for full details) to better understand both the catalyst/substrate excitation process as well as to quantify the energetics of the reaction pathway leading from $1 \mathbf{1 a}$ and phenylacetylene (3a) to 2a (Scheme 6B). In contrast to the experimentally reported value of $49.2 \mathrm{kcal} / \mathrm{mol},{ }^{26}$ we computed the relative energies of the low-lying triplet states of PC5 in the range of $65.2-77.1 \mathrm{Kcal} / \mathrm{mol}$, which would be suitable for an energy transfer process to substrate 1a ( $\mathrm{E}_{\mathrm{T}}=69.8 \mathrm{Kcal} / \mathrm{mol}$ ) (Scheme 6B1 and 6B2). The strong discrepancy between experimental and theoretical triplet energy values for PC5 may arise from drastically different environments, where experimental measurements were made on single-layer materials developed for yellow light emissions ${ }^{26}$ while the computations emulate reactions performed in solution. Indeed, triplet energies computed with and without an implicit solvent model differ significantly (by $\sim 10 \mathrm{kcal} / \mathrm{mol}$, see SI for details), indicative of the potential influence of different immediate environments. Computing the triplet energies of the other catalysts used during optimization showed a good correlation with the observed conversions, the lower yields for PC1 and PC3 being due to the formation of side product 2a1 (Scheme 6B3). After the energy transfer event, strain-release-induced bond cleavage of 1a can occur with a low activation energy, leading to ring-opened triplet bi-radical ( $\mathbf{I n t 1}_{\mathbf{T}}$ ), which is $24.7 \mathrm{Kcal} / \mathrm{mol}$ more stable than the excited state of $\mathbf{1 a}\left(\mathbf{1 a}_{\mathbf{T}}\right)$. From this point on, the reaction can proceed readily via a step-wise radical addition process to form first biradical Int3 T. In this intermediate, a favorable $^{\text {. }}$ $\pi-\pi$ interaction between the aryl rings may occur, which can potentially rationalize the observed regio and diastereoselectivity. Finally, intersystem crossing and radical recombination leads to product $2 \mathbf{2 a}$.
In conclusion, we have developed a photocatalyzed method to promote homolytic cleavage of aromatic carbonyl cyclopropanes and cyclobutanes in the absence of metal coordination. Both ethynylarenes and styrenes can be used for the [ $2 \sigma+2 \pi]$ cycloaddition. Furthermore, the catalytic system can be applied for the synthesis of bicyclo[3.1.1]heptanes via $[2 \sigma+2 \sigma]$ cycloaddition in presence of diphenyl hydrogen phosphate (PA) as co-catalyst. The obtained products are potentially useful bioisosteres of $1,2,4,5$ tetra-substituted arenes. Based on radical trapping experiments and computation, a 1,3 biradical is proposed to be the key intermediate for this transformation. Our study therefore highlights the potential of an energy transfer approach for the general activation of arylcarbonyl substituted cyclopropanes. Due to the high demand for structurally diverse ring systems and bioisosteres in drug discovery, we believe that
our study will be of high interest for both synthetic and medicinal chemists.

## ASSOCIATED CONTENT

Supporting Information: General methods, experimental procedures, characterization data and NMR spectra for new compounds.

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## Author Contributions

T.V.T. N. planned the research and performed the experiments, prepared the material for the redaction of the manuscript and the supporting information. A. B. performed preliminary studies on the $[3 \sigma+2 \pi]$ cycloaddition and participated to the investigation of the scope of the $[3 \sigma+2 \sigma]$ cycloaddition. M. D. W performed the DFT computations and prepared the supporting material for computation. J. W. supervised the research, participated to the redaction and edition of the manuscript, as well as proof-read the supporting information. All authors have given approval to the final version of the manuscript.

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# Photocatalyzed $[2 \sigma+2 \sigma]$ and $[2 \sigma+2 \pi]$ cycloadditions for the synthesis of bicyclo[3.1.1]heptanes and 5- or 6-membered carbocycles 

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## General methods

For quantitative flash chromatography, distilled technical grade solvents were used. THF, $\mathrm{Et}_{2} \mathrm{O}$, toluene, hexane and $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ were dried by passage over activated alumina under nitrogen atmosphere $\left(\mathrm{H}_{2} \mathrm{O}\right.$ content $<7$ ppm, Karl-Fischer titration). All chemicals were purchased and used as received unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, $60 \AA$, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC plastic or aluminium plates and visualized with UV light ( 254 and 366 nm ), and permanganate stain. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ${ }^{1} \mathrm{H}$-NMR spectra were recorded at room temperature on a Brucker DPX-400 400 MHz spectrometer in $\mathrm{CDCl}_{3}$, acetone- $d_{6}, \mathrm{CD}_{3} \mathrm{CN}$ or $\mathrm{CD}_{3} \mathrm{OD}$, all signals are reported in ppm and are calibrated on the residual peak of the deuterated solvent $\left(\mathrm{CDCl}_{3}: \delta_{H}=7.26 \mathrm{ppm}\right.$, acetone- $\left.\mathrm{d}_{6}: \delta_{H}=2.09 \mathrm{ppm}, \mathrm{CD}_{3} \mathrm{CN}: \delta_{H}=1.94 \mathrm{ppm}, \mathrm{CD}_{3} \mathrm{OD}: \delta_{H}=3.34 \mathrm{ppm}\right)$. The data is being reported as ( $\mathrm{s}=$ singlet, $\mathrm{d}=$ doublet, $\mathrm{t}=$ triplet, $\mathrm{q}=$ quadruplet, $\mathrm{p}=$ quintet, $\mathrm{m}=$ multiplet or unresolved, $\mathrm{br}=$ broad signal, integration, coupling constant(s) in Hz , interpretation). ${ }^{13} \mathrm{C}-\mathrm{NMR}$ spectra were recorded with 1 H -decoupling on a Brucker DPX-400 101 MHz spectrometer in $\mathrm{CDCl}_{3}$, Acetone- $d_{6}, \mathrm{CD}_{3} \mathrm{CN}$ or $\mathrm{CD}_{3} \mathrm{OD}$, all signals are reported in ppm and are calibrated on the residual peak of the deuterated solvent $\left(\mathrm{CDCl}_{3}: \delta_{\mathrm{c}}=77.0 \mathrm{ppm}\right.$, acetone- $\mathrm{d}_{6}$ : $\delta_{\mathrm{c}}=29.8 \mathrm{ppm}, \mathrm{CD}_{3} \mathrm{CN}$ : $\delta_{\mathrm{c}}=1.3 \mathrm{ppm}$, $\left.\mathrm{CD}_{3} \mathrm{OD}: \delta_{\mathrm{C}}=49.0 \mathrm{ppm}\right)$. Infrared spectra were recorded on a JASCO FT-IR B4100 or a Bruker Alpha$P$ spectrophotometer with an ATR device and a ZnSe prism and are reported as $\mathrm{cm}^{-1}$ ( $\mathrm{w}=$ weak, $\mathrm{m}=$ medium, $s=$ strong). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurements were done on a Agilent 1260 Infinity autosampler using a CHIRALPAK IA, IB, IC or IF column from DAICEL Chemical. The specific solvents and concentrations (in $\mathrm{g} / 100 \mathrm{~mL}$ ) are indicated.

All photocatalyzed reactions were carried out in oven dried glassware and under inert atmosphere (freeze pump thaw solvent stored on molecular sieves and under argon for maximum one week) unless specified otherwise. The reaction vials were placed on a stirring plate with Kessil lamps ( $440 \mathrm{~nm}, 40 \mathrm{~W}$ ) (the hood was free and coated with aluminum foil for personal protection). The distance between the Kessil lamps and the vials was approximatively 10 cm . Long irradiation resulted in temperature increasing up to $50^{\circ} \mathrm{C}$ during overnight reactions unless a fan was used in which case the temperature raised to $30-35^{\circ} \mathrm{C}$.

Photochemical experimental set-ups


## Synthesis of cyclopropanes




1a



1 g


11



1 n


1 s


1w


6a


6b


8

General procedure A:


Following a reported procedure, ${ }^{1}$ an aryl magnesium bromide solution in $\mathrm{Et}_{2} \mathrm{O}(22.0 \mathrm{mmol}, 1.1$ equiv.) was added dropwise to a solution of 3-methylbut-2-enal ( $\mathbf{S 1}, 1.91 \mathrm{~mL}, 20.0 \mathrm{mmol}$ ) in dry THF ( 30 mL ) under nitrogen, at $0^{\circ} \mathrm{C}$. The reaction mixture was stirred at room temperature until full conversion of 3 -methylbut-2-enal as indicated by TLC analysis. The reaction was quenched by addition of water ( 50 $\mathrm{mL})$. The aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 30 \mathrm{~mL})$. The combined organics were washed with brine, dried under $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated in vacuo to obtain the product $\mathbf{S 2}$ that was used directly for next step with no further purification.

To a solution of crude $\mathbf{S} 2$ in $\mathrm{Et}_{2} \mathrm{O}(120 \mathrm{~mL})$ was added $\mathrm{MnO}_{2}$ (20 equiv.). The mixture was then stirred for 16 h at room temperature. Then the reaction mixture was filtered over a pad of Celite ${ }^{\mathrm{TM}}$ and the solvent was removed under reduced pressure to afford S3 that was used with no further purification.

An oven-dried round-bottom flask was charged with potassium tert-butoxide (1.2 equiv.) and trimethylsulfoxonium iodide ( 1.2 equiv.). DMSO ( $3.5 \mathrm{~mL} / \mathrm{mmol}$ ) was then added dropwise and the reaction mixture was then stirred until full dissolution of the reactants $\mathbf{S 3}$ (1.0 equiv.) dissolved in DMSO $(2.0 \mathrm{~mL} / \mathrm{mmol})$ was then added dropwise and the reaction mixture was stirred at room temperature for 4 hours. Water was slowly added and the aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 30 \mathrm{~mL})$. The combined organics were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated in vacuo to afford the crude product that was further purified by flash column chromatography to obtain the corresponding cyclopropanes.

## General procedure B:



S6 is commercially available and was used as received. Otherwise, the synthesis follows a modified reported procedure, ${ }^{2}$ to an oven-dried three-neck round-bottom flask connected with a thermometer, under nitrogen, was added LiHMDS ( 1 M in THF, 2.2 equiv.). At $0^{\circ} \mathrm{C}$, diethyl methylphosphonate ( 1.1 equiv.) was added dropwise. Then, methyl benzoate $\mathbf{S 5}$ ( 1.0 equiv.) was added dropwise, while keeping the internal temperature below $5^{\circ} \mathrm{C}$. After full consumption of the ester, (ca. 1 h ), still at $0^{\circ} \mathrm{C}$, the reaction mixture was quenched with a saturated solution of $\mathrm{NH}_{4} \mathrm{Cl}$. The aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (gradient pentane/EA, 30-85\% EA) to afford diethyl (2-oxo-2-phenylethyl) phosphonate $\mathbf{S 6}$ in an impure mixture and directly used for the next step without further purification. The HWE reaction was performed using a modified literature procedure. ${ }^{1}$ An oven-dried round-bottom flask was charged with KOtBu (1.0 equiv.). Under nitrogen, S6 ( 1.0 equiv.) and THF ( 0.30 M ) were added. The mixture was stirred at room temperature for 2 hours. The flask was then equipped with a reflux condenser and the reaction mixture was heated to reflux for 48 hours. The reaction mixture was then filtered and diluted with $\mathrm{Et}_{2} \mathrm{O}$, followed by brine. The aqueous layer was extracted three times with $\mathrm{Et}_{2} \mathrm{O}$, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated in vacuo. The crude mixture was purified by flash column chromatography on Biotage (Büchi flashpure cartridge 40 g , gradient of pentane:ethyl acetate from 100:0 to 95:5) to remove unreacted ketone and phosphonate. Compound S7 was used with no further characterization.
An oven-dried round-bottom flask was charged with potassium tert-butoxide (1.2 equiv.) and trimethylsulfoxonium iodide ( 1.2 equiv.). DMSO ( $3.5 \mathrm{~mL} / \mathrm{mmol}$ ) was then added dropwise and the reaction mixture was then stirred until full dissolution of the reactants. $\mathbf{S 7}$ (1.0 equiv., calibrated from S6) dissolved in DMSO ( $2.0 \mathrm{~mL} / \mathrm{mmol}$ ) was then added dropwise and the reaction mixture was stirred at room temperature for 4 hours. Water was slowly added and the aqueous layer was extracted with
$\mathrm{Et}_{2} \mathrm{O}$ (3 times). The combined organics were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated in vacuo to afford the crude product that was further purified by flash column chromatography to obtain the corresponding cyclopropanes.

## General procedure C



Following a reported procedure, ${ }^{3} 3$-chloropropionyl chloride ( 1.1 equiv) was added dropwise to a suspension of aluminum chloride ( 1.2 equiv) in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(1.20 \mathrm{M})$, at $0^{\circ} \mathrm{C}$, followed by the addition of substituted arenes $\mathbf{S 9}$ (1.0 equiv). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC until full conversion of S9. Then, crushed ice was slowly added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ (3 times). The combined organic layers were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and the crude mixture was evaporated under reduced pressure. The resulting residue of $\mathbf{S 1 0}$ was used directly for the next step.

Following a reported procedure, ${ }^{4}$ to a solution of $\mathbf{S 1 0}$ (1.0 equiv.), $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( 1.0 equiv.), KI ( 0.1 equiv.) in acetone, dimethyl malonate ( 2.5 equiv.) was added and the reaction mixture was stirred at $25^{\circ} \mathrm{C}$ overnight. The reaction was monitored by TLC until full conversion then the mixture was filtered off and filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography or by chromatography of Biotage (Gradient ethyl acetate/pentanes from $1: 4$ to 1:8) to obtain product S11.

Following reported procedure, ${ }^{5 a}$ to a solution of $\mathbf{S} 11$ in ethanol $(0.10 \mathrm{M}), \mathrm{I}_{2}$ ( 1.0 equiv) was added, followed by the addition of DBU (2.0 equiv.) The reaction was stirred at $35^{\circ} \mathrm{C}$ until full conversion of S 11 was indicated by TLC. The mixture was then evaporated in vacuo. Saturated $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$ was added to the mixture until the disappearance of dark color, the mixture was then extracted with dichloromethane ( 3 times). The combined organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated under reduced pressured. The residue was purified by chromatography on Biotage (Gradient ethyl acetate/pentanes 10:90 to $30: 70$ ) to provide the corresponding cyclopropanes.

## (2,2-Dimethylcyclopropyl)(phenyl)methanone (1a)



Following general procedure A, starting from 3-methylbut-2-enal ( $20.0 \mathrm{mmol}, 1.91 \mathrm{~mL}, 1.00$ equiv.). The crude mixture was purified by flash column chromatography on Biotage (Büchi flashpure cartridge 80 g , gradient of pentane:ethyl acetate from 100:0 to 97:3) affording (2,2-dimethylcyclopropyl) (phenyl)methanone ( $\mathbf{1 a}, 2.12 \mathrm{~g}, 12.2 \mathrm{mmol}, 61 \%$ over 3 steps) as a colorless liquid. ${ }^{\mathbf{1}} \mathrm{H}$ NMR ( 400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.97-7.92(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.57-7.52(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.50-7.44(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 2.48(\mathrm{dd}$, $J=7.5,5.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $1.52\left(\mathrm{dd}, J=5.7,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.36\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 1.09(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{CCH}_{3}$ ), 0.96 (dd, $J=7.5,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 198.8,139.2$, 132.6, 128.6, 128.1, 33.0, 27.2, 27.1, 22.1, 18.6.

NMR data matching literature. ${ }^{1}$


Following general procedure $\mathbf{C}$, starting with $\mathbf{S 1 0}$ as 3 -chloropropiophenone ( $1.68 \mathrm{~g}, 10.0 \mathrm{mmol}, 1.00$ equiv.) affording dimethyl 2-benzoylcyclopropane-1,1-dicarboxylate 1b ( $1.10 \mathrm{~g}, 4.20 \mathrm{mmol}, 42 \%$ over 2 steps). TLC: $\mathrm{R}_{\mathrm{f}}=0.56\left(\mathrm{SiO}_{2} 70: 30\right.$ hexane: $\left.\mathrm{Et}_{2} \mathrm{O}\right)$
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.0-8.0(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.7-7.6(\mathrm{~m}, 1 \mathrm{H}, \operatorname{ArH}), 7.5-7.5(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 3.8(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), $3.7\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.6(\mathrm{dd}, J=8.6,6.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.2(\mathrm{dd}, J=6.9,4.3 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CHCH}_{2}$ ), 1.8 (dd, $J=8.6,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 195.0,169.7,166.6$, 137.2, 133.7, 128.9, 128.6, 53.5, 53.0, 39.2, 31.2, 21.3.

NMR data matching literature. ${ }^{11}$

## Dimethyl 2-(4-(methoxycarbonyl)benzoyl)cyclopropane-1,1-dicarboxylate (1c)



Following general procedure $\mathbf{C}$, starting with $\mathbf{S 1 0}$ as methyl 4-(3-chloropropanoyl)benzoate ( 1.13 g . $5.00 \mathrm{mmol}, 1.0$ equiv). afforded $\mathbf{1 c}$ ( $576 \mathrm{mg}, 1.80 \mathrm{mmol}, 36 \%$ over 2 steps). ${ }^{1} \mathbf{H} \mathbf{N M R}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ $\delta 8.14(\mathrm{~d}, J=8.5,2 \mathrm{H}, \mathrm{ArH}), 8.04(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 3.96\left(\mathrm{~s}, \mathrm{OCH}_{3}\right), 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.69(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), 3.54 (dd, $J=8.6,6.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}$ cyclopropane), 2.24 (dd, $J=6.9,4.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ cyclopropane), 1.81 (dd, $J=8.6,4.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ cyclopropane). NMR data matching literature. ${ }^{11}$

## (2,2-difluorocyclopropyl)(phenyl)methanone (1d)



Following a modified literature procedure, ${ }^{55}$ to a shlenk flask was added the vinyl ketone $\mathbf{S 1 2}$ ( 5.0 mmol , 660 mg . 1.0 equiv.) together with sodium fluoride ( $0.5 \mathrm{mmol}, 21.0 \mathrm{mg}, 0.10$ equiv.). $m$-xylene was added under nitrogen atmosphere and the reaction mixture was heated to $110^{\circ} \mathrm{C}$. Then, trimethylsilyl-2,2-difluoro-2-(fluorosulphonyl)acetate $\mathbf{S 1 3}$ ( $10 \mathrm{mmol}, 2.00 \mathrm{ml}, 2.0$ equiv.) was added dropwise over 30 minutes and the reaction mixture was stirred for 30 more minutes at $110^{\circ} \mathrm{C}$. After full conversion was observed by TLC, the crude mixture was concentrated and purified by flash column chromatography on Biotage (Büchi flashpure cartridge 25 g , gradient of pentane:ethyl acetate from $100: 0$ to $97: 3$ ) affording the (2,2-difluorocyclopropyl)(phenyl)methanone ( $500.50 \mathrm{mg}, 2.750 \mathrm{mmol}, 55 \%$ ) as a paleyellow liquid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.04-7.99$ (m, 2H), $7.66-7.59$ (m, 1H), $7.56-7.48$ (m, 2H), 3.39 (ddd, $J=13.5,10.4,7.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.43 (dtd, $J=12.2,7.8,5.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.81 (dddd, $J=11.7,10.4,7.6,4.8$ $\mathrm{Hz}, 1 \mathrm{H}$ ). ${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-124.32$ (dddd, $J=148.5,13.4,11.5,5.7 \mathrm{~Hz}$ ), -140.19 (ddd, $J=$ $148.5,12.2,4.8 \mathrm{~Hz}$ ). Data matching with literature ${ }^{5 b}$
(2,2-Dimethylcyclopropyl)(o-tolyl)methanone (1e)


Following general procedure A, starting from 3-methylbut-2-enal ( $10 \mathrm{mmol}, 0.97 \mathrm{~mL}, 1.0$ equiv.). The crude mixture was purified by flash column chromatography on Biotage (Büchi flashpure cartridge 80 g , gradient of pentane:ethyl acetate from 100:0 to $97: 3$ ) affording (2,2-dimethylcyclopropyl) (otolyl)methanone $\mathbf{1 e}(639 \mathrm{mg}, 3.40 \mathrm{mmol}, 34 \%$ over 3 steps).
TLC: $\mathrm{R}_{\mathrm{f}}=0.49\left(\mathrm{SiO}_{2} 80: 20\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.59(\mathrm{dd}, J=7.6,1.5 \mathrm{~Hz}$, 1H, ArH), 7.38-7.33 (m, 1H, ArH), 7.31-7.17 (m, 2H, ArH), 2.50 (s, 3H, ArCH3), 2.28 (dd, J = 7.5, $5.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 1.52\left(\mathrm{dd}, J=5.6,4.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.34\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 1.19\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right)$, 0.96 (dd, $\left.J=7.4,4.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 203.0, 140.6, 137.1, 131.6, 130.7, $128.5,125.8,36.2,27.9,27.2,23.0,20.7,18.5$. NMR data matching literature. ${ }^{1}$

## (2,2-Dimethylcyclopropyl)(4-methoxyphenyl)methanone (1f)



Following general procedure A, starting from 3-methylbut-2-enal ( $10 \mathrm{mmol}, 0.95 \mathrm{~mL}, 1.0$ equiv.). The crude mixture was purified by flash column chromatography on Biotage (Büchi flashpure cartridge 40 g , gradient of pentane:ethyl acetate from 100:0 to 90:10) affording (2,2-dimethylcyclopropyl) (4methoxyphenyl)methanone $1 \mathrm{f}(1.13 \mathrm{~g}, 5.54 \mathrm{mmol}, 55 \%$ over 3 steps) as a colorless oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.37$ (silica $92: 8$ pentane: $\mathrm{Et}_{2} \mathrm{O}$ ). ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.00-7.89(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.02-$ $6.89(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 3.87\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.43(\mathrm{dd}, J=7.5,5.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 1.48$ (dd, $J=5.6$, $4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $1.34\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 1.06\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 0.91\left(\mathrm{dd}, J=7.5,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right)$. ${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 197.2,163.2,132.3,130.4,113.7,55.6,32.6,27.2,26.3,21.6,18.7$. IR $\left(v_{\text {max }}, \mathrm{cm}^{-1}\right) 3000(\mathrm{w}), 2946(\mathrm{~m}), 2878(\mathrm{w}), 2846$ (w), 1660 (s), 1605 (s), 1577 (m), 1510 (m), 1461 (m), 1422 (m), 1390 (s), 1311 (m), 1260 (s), 1225 (s), 1177 (s), 1117 (m), 1033 (m), 997 (m), 914 (m), $852(\mathrm{~m}), 824(\mathrm{w}), 803(\mathrm{~m}), 738(\mathrm{w})$. HRMS (ESI/QTOF) m/z: [M+H]+ Calcd for $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{O}_{2}{ }^{+}$ 205.1223; Found 205.1228.

## (2,2-Dimethylcyclopropyl)(4-fluorophenyl)methanone (1g)



Following general procedure $\mathbf{A}$, starting from 3-methylbut-2-enal ( $8.0 \mathrm{mmol}, 0.76 \mathrm{~mL}, 1.00$ equiv.). The crude mixture was purified by flash column chromatography on Biotage (Büchi flashpure cartridge 40 g, gradient of pentane:ethyl acetate from 100:0 to 97:3) affording (2,2-dimethylcyclopropyl)(4fluorophenyl)methanone 1 g ( $0.90 \mathrm{~g}, 4.7 \mathrm{mmol}, 59 \%$ over 3 steps) as a pale yellow liquid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.38$ (silica $98: 2$ pentane: $\mathrm{Et}_{2} \mathrm{O}$ ). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.00-7.93(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.17-7.10(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 2.42$ (dd, $J=7.5,5.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 1.51 (dd, $J=5.6,4.1 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CHCH}_{2}$ ), $1.35\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 1.08\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 0.96$ (dd, $\left.J=7.5,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 197.1,165.5(\mathrm{~d}, ~ J=253.5 \mathrm{~Hz}$ ), 135.6 (d, $J=2.9 \mathrm{~Hz}$ ), $130.7(\mathrm{~d}, J=9.2 \mathrm{~Hz})$, $115.6(\mathrm{~d}, \mathrm{~J}=21.8 \mathrm{~Hz}), 32.8,27.2,27.1,22.2,18.6 .{ }^{19} \mathbf{F} \mathbf{N M R}\left(376 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta-106.6 . \operatorname{IR}\left(v_{\max }, \mathrm{cm}\right.$
${ }^{1}$ ) 3000 (w), 2957 (w), 2930 (w), 2878 (w), 1670 (s), 1599 (s), 1509 (m), 1458 (w), 1412 (m), 1383 (m), 1270 (m), 1224 (s), 1159 (m), 1116 (m), 1091 (w), 1040 (w), 1001 (s), 914 (w), 857 (m), $809(\mathrm{~m})$. HRMS (ESI/QTOF) m/z: [M+H]+ Calcd for $\mathrm{C}_{12} \mathrm{H}_{14} \mathrm{FO}^{+} 193.1023$; Found 193.1030.

## (2,2-dimethylcyclopropyl)(4-(trifluoromethyl)phenyl)methanone (1h)



Following general procedure A, starting from 3-methylbut-2-enal ( $10 \mathrm{mmol}, 0.95 \mathrm{~mL}, 1.00$ equiv.). The crude mixture was purified by flash column chromatography on Biotage (Büchi flashpure cartridge 40 g , gradient of pentane:ethyl acetate from 100:0 to 95:5) affording (2,2-dimethylcyclopropyl)(4fluorophenyl)methanone $\mathbf{1 h}(1.186 \mathrm{mg}, 4.90 \mathrm{mmol}, 49 \%$ over 3 steps) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCI3) б 8.03 (d, J = $8.1 \mathrm{~Hz}, 1 \mathrm{H}, ~ \mathrm{ArH}$ ), 7.73 (d, J = $8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 2.47 (dd, $\mathrm{J}=7.4,5.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 1.56 (dd, J = $\left.5.7,4.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.38(\mathrm{~s}, 3 \mathrm{H}), 1.10(\mathrm{~s}, 3 \mathrm{H})$, $1.02\left(\mathrm{dd}, \mathrm{J}=7.5,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .19^{\mathrm{F}} \mathrm{NMR}\left(377 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta-62.98$. NMR data matching literature. ${ }^{16}$

## Tert-butyl 2-benzoylcyclopropane-1-carboxylate (1i)



Following a reported procedure, ${ }^{9}$ to a stirred solution of phenacyl chloride $\mathrm{S} 14(1.55 \mathrm{~g}, 10.0 \mathrm{mmol}, 1.00$ equiv.) in dry $\mathrm{MeCN}(0.25 \mathrm{M}$ ) was added DABCO ( $1.10 \mathrm{~mL}, 10.0 \mathrm{mmol}, 1.0$ equiv.). The mixture was stirred at room temperature for 30 minutes followed by the addition of $\mathrm{NaOH}(600 \mathrm{mg}, 15.0 \mathrm{mmol}, 1.5$ equiv). After that, $t$-butyl acrylate ( $0.21 \mathrm{~mL}, 10 \mathrm{mmol}, 1$ equiv.) was added and the mixture was heated to $80^{\circ} \mathrm{C}$. The reaction was monitored by TLC analysis until the disappearance of the alkene. The mixture was quenched by saturated aqueous ammonium chloride solution ( 30 mL ) and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 30 \mathrm{~mL})$. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and the solvent was evaporated in rotavap. The residue was purified by Biotage (Gradient ethyl acetate/pentanes from $1 / 10$ to 1:4) to provide the corresponding cyclopropanes $\mathbf{1 i}\left(1.62 \mathrm{~g}, 6.60 \mathrm{mmol}, 66 \%\right.$ yield) as white solid. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) б $8.1-8.0(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7. -7.6 (m, 1H, ArH), 7.5-7.5 (m, 2H, ArH), 3.1 (ddd, $J=$ $8.6,5.7,3.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.3 (ddd, $\left.J=8.7,5.9,3.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCO}_{2}\left(\mathrm{CH}_{3}\right)_{3}\right), 1.6-1.5(\mathrm{~m}, 2 \mathrm{H}$, $\left.\mathrm{CHCH}_{2}\right), 1.5\left(\mathrm{~s}, 9 \mathrm{H}, \mathrm{CO}_{2}\left(\mathrm{CH}_{3}\right)_{3}\right) .{ }^{13} \mathrm{C}$ NMR (101 MHz, $\left.\mathrm{CDCl}_{3}\right)$ ס 197.5, 171.6, 137.3, 133.4, 128.8, 128.4, 81.4, 28.2, 25.9, 25.9, 18.0. NMR data matching literature. ${ }^{9}$

## Trans-phenyl(2-phenylcyclopropyl)methanone (1j)



Following general procedure $\mathbf{A}$, starting from trans-chalcone as $\mathbf{S 3}$ ( $6.00 \mathrm{mmol}, 1.25 \mathrm{~g}, 1.0$ equiv.). The crude mixture was purified by flash column chromatography on Biotage (Büchi flashpure
cartridge 40 g , gradient of pentane:ethyl acetate from 100:0 to 95:5) affording trans-phenyl(2-phenyl-cyclopropyl) methanone $1 \mathrm{j}(1.22 \mathrm{~g}, 5.50 \mathrm{mmol}, 91 \%)$ as a white crystalline solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.02-7.98(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.59-7.54(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.50-7.43(\mathrm{~m}, 2 \mathrm{H}$, ArH), 7.35-7.29 (m, 2H, ArH), 7.26-7.21 (m, 1H, ArH), 7.21-7.17 (m, 2H, ArH), 2.91 (ddd, J = $8.0,5.3,4.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.71 (ddd, $J=9.0,6.6,4.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCH}$ ), 1.94 (ddd, $J=9.2$, $5.3,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.57 (ddd, $J=8.0,6.6,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( 101 MHz , $\mathrm{CDCl}_{3}$ ) $\delta$ 198.7, 140.6, 137.9, 133.1, 128.7, 128.3, 126.7, 126.4, 30.2, 29.5, 19.4. 1 carbon unresolved. NMR data matching literature. ${ }^{8 \mathrm{a}}$

## Phenyl((1R,2R)-2-(trifluoromethyl)cyclopropyl)methanone (1k)

$\mathrm{Ph}_{2} \mathrm{~S}+$




Following reported procedure, ${ }^{6 b}$ a seal-cap microwave vial containing 2,2,2-trifluoroethyl triflate ( 0.464 $\mathrm{g}, 2 \mathrm{mmol}, 1.0$ equiv.) and diphenyl sulfide ( $1.8 \mathrm{~g}, 10 \mathrm{mmol}, 5.0$ equiv.) was stirred at $150^{\circ} \mathrm{C}$ overnight. After that, the reaction mixture was cooled to room temperature then diethyl ether was added and the precipitate was washed with diethyl ether to obtain the product diphenyl(2,2,2-trifluoroethyl)sulfonium triflate. The product was used directly to the next step without further purification. TBAF ( $3.0 \mathrm{mmol}, 3.0$ $\mathrm{mL}, 1.5$ equiv.) was added dropwise under $\mathrm{N}_{2}$ atmosphere into the mixture of diphenyl( $2,2,2$ trifluoroethyl)sulfonium triflate ( $2 \mathrm{mmol}, 83.7 \mathrm{mg}, 1.0$ equiv.), Vinyl phenyl ketone ( $4.0 \mathrm{mmol}, 5.28 \mathrm{mmol}$, 2.00 equiv.) and $4 \AA$ MS ( 1600 mg ) in dichloromethane $(20.0 \mathrm{~mL})$. The reaction mixture was stirred at room temperature for overnight. After concentration, the product was purified by Biotage (Büchi flashpure cartridge 25 g , gradient of pentane:ethyl acetate from 100:0 to 95:5) as the eluent to afford the final product $\mathbf{1 k}$ ( $265.30 \mathrm{mg}, 1.239 \mathrm{mmol}, 62 \%$ ) as colorless oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.3$ (silica pentane). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.02$ (dd, $J=8.1,1.4 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), 7.69 $7.60(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.52(\mathrm{t}, J=7.7 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 3.03$ (dt, $J=9.3,4.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.36$ (dtd, $J=$ $9.1,6.5,4.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CF}_{3} \mathrm{CH}$ ), 1.53 (dt, $J=9.3,5.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.43 (ddd, $J=8.8,6.1,4.6 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 196.55, 136.89, 133.79, 128.94, 128.42, 128.0 (q, J=271.7 $\mathrm{Hz}), 24.00(\mathrm{q}, J=37.9 \mathrm{~Hz}), 20.22(\mathrm{q}, J=2.2 \mathrm{~Hz}), 12.71(\mathrm{q}, J=2.7 \mathrm{~Hz}) .19^{\mathrm{F}} \mathrm{NMR}(376 \mathrm{MHz}, \mathrm{CDCl} 3) \delta$ -66.79 (d, J = 6.6 Hz, 3F). IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2961 (w), 1736 (m), 1679 (m), 1599 (w), 1451 (w), 1348 (s), 1266 (s), 1153 (s). HRMS (APCI/QTOF) m/z: [M + H] ${ }^{+}$Calcd for $\mathrm{C}_{11} \mathrm{H}_{10} \mathrm{~F}_{3} \mathrm{O}^{+} 215.0678$; Found 215.0675.

Phenyl(spiro[2.5]octan-1-yl)methanone (1I)


Following general procedure B, starting from cyclohexanone ( $1.5 \mathrm{mmol}, 0.16 \mathrm{~mL}, 1.00$ equiv.). The crude mixturewas purified by flash column chromatography on Biotage (Büchi flashpure cartridge 25 g , gradient ofpentane:ethyl acetate from 100:0 to 97:3) affording phenyl(spiro[2.5]octan-1-yl)methanone 11 ( $91 \mathrm{mg}, 0.43 \mathrm{mmol}, 27 \%$ over 2 steps) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.03-7.99$ ( $\mathrm{m}, 2 \mathrm{H}, \mathrm{ArH}$ ), 7.56-7.51 (m, 1H, ArH), 7.49-7.44 (m, 2H, ArH), 2.51 (dd, J = 7.4, $5.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 1.69-1.41 (m, 10H, cyclohexyl CH), 1.22-1.16 (m, 1H, $\mathrm{CHCH}_{2}$ ), 0.94 (dd, $J=7.3,4.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 198.3,139.1,132.5$, $128.6,128.1,37.9,35.5,32.2,28.4,26.3,26.1,26.0,21.4$. NMR data matching literature. ${ }^{10}$

## Phenyl(spiro[2.3]hexan-1-yl)methanone (1m)



Following general procedure $\mathbf{B}$, starting from cyclobutanone ( $0.37 \mathrm{~mL}, 5.0 \mathrm{mmol}, 1.0$ equiv.). The crude mixture was purified by flash column chromatography on Biotage (Büchi flash pure cartridge 40 g , gradientof pentane:ethyl acetate from 100:0 to 97:3) affording phenyl(spiro[2.3]hexan-1-yl)methanone 1 m ( $447 \mathrm{mg}, 2.40 \mathrm{mmol}, 48 \%$ over 2 steps) as a colorless oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.32$ (silica $98: 2$ pentane:Et ${ }_{2} \mathrm{O}$ ). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.03-7.96(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.59-$ $7.53(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.52-7.45(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 2.67(\mathrm{dd}, \mathrm{J}=8.0,5.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.40-2.33(\mathrm{~m}$ 1 H , cyclobutyl CH), 2.25-2.17 (m, 2H, cyclobutyl CH), 2.14-2.03 (m, 2H, cyclobutyl CH), 2.03-1.90 (m, 1H, cyclobutyl CH), 1.59 (dd, $J=5.4,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.22-1.17 (m, 1H, CHCH2). ${ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 198.5,139.0,132.6,128.6,128.0,35.4,31.2,30.6,27.7,22.9,16.8 . \mathbf{I R}^{( } v_{\text {max }}, \mathrm{cm}^{-}$ ${ }^{1}$ ) 3065 (w), 2989 (w), 2950 (m), 2852 (w), 1664 (s), 1602 (w), 1584 (w), 1447 (m), 1429 (w), 1390 (s), 1326 (w), 1249 (m), 1220 (s), 1105 (w), 1053 (m), 1025 (m), 964 (w), 832 (w), 777 (w), 714 (s). HRMS (ESI/QTOF) m/z: [M+H]+ Calcd for $\mathrm{C}_{13} \mathrm{H}_{15} \mathrm{O}^{+}$187.1117; Found 187.1122.

## (2,2-Dimethylcyclopropyl)(naphthalen-2-yl)methanone (1n)



Following a reported procedure, ${ }^{6 a}$ magnesium ( 1.2 equiv.) together with $I_{2}(0.5 \mathrm{~mol} \%$ ) were added to an oven-dried three-neck round-bottom flask equipped with a reflux condenser. Anhydrous THF was added. Under nitrogen atmosphere, 2-bromonaphthalene $\mathbf{S 1 6}(10.0 \mathrm{mmol}, 2.07 \mathrm{~g}, 1.0$ equiv.) solution in dry THF ( 1 M ) was added dropwise and the reaction mixture was heated to reflux for 6 hours. The reaction was then cooled to room temperature and 3-methylbut-2-enal ( $8.3 \mathrm{mmol}, 0.79 \mathrm{~mL}, 0.8$ equiv.) solution in dry THF ( 1 M ) was added dropwise and the mixture was left to stir for two more hours until full conversion of the aldehyde. The reaction was then cooled at $0{ }^{\circ} \mathrm{C}$ and quenched with a saturated solutionof $\mathrm{NH}_{4} \mathrm{Cl}$. The aqueous layer was extracted three times with $\mathrm{Et}_{2} \mathrm{O}(3 \times 30 \mathrm{~mL})$, washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated in vacuo. The crude $\alpha-\beta$ unsaturated alcohol was converted into the desired cyclopropane using general procedure $A$. The crude mixture was purified by flash column chromatography on Biotage (Büchi flashpure cartridge 40 g , gradient of pentane:ethyl acetate from 100:0 to 95:5) affording (2,2-dimethylcyclopropyl)(naphthalen-2yl)methanone $1 \mathrm{n}(1.37 \mathrm{~g}, 6.10 \mathrm{mmol}, 73 \%$ over 4 steps$)$ as a white crystalline solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.35$ (silica $98: 2$ pentane: $\mathrm{Et}_{2} \mathrm{O}$ ). Mp: 62-63 ${ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.48-8.45(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 8.03(\mathrm{dd}, \mathrm{J}=8.6,1.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 8.01-7.97$ (m, 1H, ArH), 7.92-7.87 (m, 2H, ArH), 7.62-7.53 (m, 2H, ArH), 2.64 (dd, J=7.5, 5.6 Hz, 1H, C(O)CH), 1.59 (dd, $J=5.6,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.43 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{CCH}_{3}$ ), 1.13 (s, 3H, CCH3), 1.01 (dd, $J=7.5$, $\left.4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 198.6,136.5,135.5,132.7,129.7,129.5,128.4$, 128.3, 127.9, 126.8, 124.2, 33.1, 27.3, 27.2, 22.3, 18.7. NMR data matching literature. ${ }^{7}$

## Trans-(2-methylcyclopropyl)(phenyl)methanone (10)



Following general procedure A, starting from 1-phenylbut-2-en-1-on as $\mathbf{S 3}(3.0 \mathrm{mmol}, 0.43 \mathrm{~mL}, 1.0$ equiv.). The crude mixture was purified by flash column chromatography on Biotage (Büchi flashpure cartridge 25 g , gradient of pentane:ethyl acetate from 100:0 to 98:2) affording trans-(2-
methylcyclopropyl) (phenyl)methanone 10 ( $297 \mathrm{mg}, 1.85 \mathrm{mmol}, 62 \%$ ) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ठ 8.02-7.96(m,2H, ArH), 7.59-7.52 (m, 1H, ArH), 7.50-7.45 (m, 2H, ArH ), 2.40 (dt, $J=8.2,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $1.64-1.56\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{3}\right), 1.49$ (ddd, $J=8.5,4.6,3.4$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.22 (d, $J=6.0 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CHCH}_{3}$ ), 0.89 (ddd, $J=7.8,6.4,3.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 200.3,138.3,132.7,128.6,128.1,26.5,21.5,20.3,18.4$. NMR data matching literature. ${ }^{8 b}$

Compound 1 p is commercially available and was used as received without further purification.

## Dimethyl 2-(4-bromobenzoyl)cyclopropane-1,1-dicarboxylate (1q)



Following general procedure C, starting from 4' bromo-3-chloropropiophenone ( $2.47 \mathrm{~g}, 10.0 \mathrm{mmol}, 1.00$ equiv.), obtained cyclopropanes 1 ( $(1.60 \mathrm{~g}, 4.70 \mathrm{mmol}, 47 \%$ over 2 steps) as pale yellow oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.24\left(\mathrm{SiO}_{2}, 90: 10\right.$ Pentane:EA). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.92-7.82(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.71-$ 7.58 (m, 2H, ArH), $3.81\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.68\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.48(\mathrm{dd}, J=8.6,6.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.22$ (dd, $\left.J=6.8,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.78\left(\mathrm{dd}, J=8.6,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C} \mathbf{N M R}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 194.0, 169.5, 166.5, 135.8, 132.2, 130.0, 129.1, 53.5, 53.1, 39.3, 31.0, 21.2. IR ( $\left.\mathrm{v}_{\mathrm{max}}, \mathrm{cm}^{-1}\right) 2957$ (w), 1736 (s), 1732 (s), 1678 (s), 1588 (m), 1443 (m), 1404 (m), 1271 (s), 1199 (m), 1130 (s). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{14} \mathrm{H}_{13} \mathrm{BrNaO}_{5}{ }^{+} 362.9839$; Found 362.9829. Data matching reported values. ${ }^{11}$

## Dimethyl 2-(4-fluorobenzoyl)cyclopropane-1,1-dicarboxylate (1r)



Following general procedure $\mathbf{C}$, starting from 4' fluoro-3-chloropropiophenone ( $1.87 \mathrm{~g}, 10.0 \mathrm{mmol}, 1.0$ equiv.), obtained cyclopropanes $1 \mathbf{r}(1.57 \mathrm{~g}, 5.60 \mathrm{mmol}, 56 \%$ over 2 steps $)$ as white crystals.

TLC: $\mathrm{R}_{\mathrm{f}}=0.21\left(\mathrm{SiO}_{2}, 90: 10\right.$ Pentane:EA). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.08-7.98(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.21-$ $7.12(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 3.81\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.69\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.50(\mathrm{dd}, \mathrm{J}=8.6,6.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.23$ (dd, $\left.J=6.9,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.78\left(\mathrm{dd}, J=8.6,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C} \mathbf{N M R}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 193.3, 169.6, 166.5, 166.2 (d, $J=255.8 \mathrm{~Hz}$ ), 133.6 (d, $J=3.0 \mathrm{~Hz}$ ), 131.3 (d, $J=9.4 \mathrm{~Hz}$ ), 116.0 (d, $J=$ $22.0 \mathrm{~Hz}), 53.5,53.1,39.2,31.0,21.2 .{ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-104.14$ (ddd, $J=13.7,8.4,5.3$ Hz ). HRMS (Sicrit plasma/LTQ-Orbitrap) m/z: $[\mathrm{M}+\mathrm{H}]^{+}$Calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{FO}_{5}{ }^{+}$281.0820; Found 281.0819. Data matching reported values. ${ }^{11}$

## Dimethyl 2-(4-methoxybenzoyl)cyclopropane-1,1-dicarboxylate (1s)



Following general procedure C, starting from 4' methoxy-3-chloropropiophenone ( $1.98 \mathrm{~g}, 10.0 \mathrm{mmol}$, 1.0 equiv.), obtained cyclopropanes $\mathbf{1 s}(1.20 \mathrm{~g}, 4.10 \mathrm{mmol}, 41 \%$ over 2 steps ) as yellow solid.

TLC: $\mathrm{R}_{\mathrm{f}}=0.25$ (silica, Pentane : EA 80:20). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.09-7.88(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.06-$ 6.89 (m, 2H, ArH), 3.88 (s, 3H, OCH3), $3.80\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.69\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{ArOCH}_{3}\right), 3.52$ (dd, J=8.7, 6.9 $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.21 (dd, $J=6.9,4.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $1.75\left(\mathrm{dd}, J=8.6,4.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 193.1,169.9,166.8,164.1,130.9,130.2,114.0,55.7,53.4,53.0,38.8,30.9$, 21.2. HRMS (Sicrit plasma/LTQ-Orbitrap) m/z: $[\mathrm{M}+\mathrm{H}]^{+}$Calcd for $\mathrm{C}_{15} \mathrm{H}_{17} \mathrm{O}_{6}{ }^{+}$293.1020; Found 293.1019. Data matching reported values. ${ }^{11}$

## Dimethyl 2-([1,1'-biphenyl]-4-carbonyl)cyclopropane-1,1-dicarboxylate (1t)



Following general procedure $\mathbf{C}$, starting from biphenyl ( $1.54 \mathrm{~g}, 10.0 \mathrm{mmol}, 1.0$ equiv.), obtained cyclopropanes 1 t ( $1.15 \mathrm{~g}, 3.40 \mathrm{mmol}, 34 \%$ over 3 steps). as sticky oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.32\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ठ $8.11-8.05(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.74-7.69(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.67-7.60(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.51-7.45(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.44-7.36(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 3.82$ (s, 3H, OCH $)_{3}$, $3.71\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.60(\mathrm{dd}, J=8.6,6.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.26(\mathrm{dd}, J=6.9,4.3 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.81 (dd, $J=8.6,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 194.4,169.7,166.6$, 146.4, 139.8, 135.8, 129.2, 129.1, 128.5, 127.5, 127.4, 53.4, 53.0, 39.2, 31.2, 21.3. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2957 (w), 1732 (s), 1673 (s), 1603 (m), 1437 (m), 1275 (s), 1216 (s), 1133 (s), 967 (m). HRMS (ESI/QTOF) $\mathrm{m} / \mathrm{z}:[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{NaO}_{5}{ }^{+}$361.1046; Found 361.1045.

## Dimethyl 2-(dibenzo[b,d]furan-2-carbonyl)cyclopropane-1,1-dicarboxylate (1u)



Following general procedure $\mathbf{C}$, starting from dibenzofurane ( $1.68 \mathrm{~g}, 10.0 \mathrm{mmol}, 1.0$ equiv.), obtained cyclopropanes $1 \mathbf{u}(774 \mathrm{mg}, 2.20 \mathrm{mmol}, 22 \%$ over 3 steps) as sticky yellow oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.32\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.64(\mathrm{dd}, J=1.9,0.6 \mathrm{~Hz}, 1 \mathrm{H}$, ArH), 8.17 (dd, $J=8.7,1.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 8.02 (ddd, $J=7.8,1.4,0.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.64 (dd, $J=8.7$, $0.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.61 (dt, $J=8.2,0.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), $7.55-7.50$ (m, 1H, ArH), 7.41 (td, $J=7.5,1.0 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{ArH}$ ), 3.84 (s, 3H, $\mathrm{OCH}_{3}$ ), 3.71 (s, 3H, OCH3), 3.71-3.67 (m, 1H, C(O)CH), 2.29 (dd, J = 6.9, 4.3 $\left.\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.87-1.81\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 194.0,169.8,166.7,159.4$, 157.1, 132.5 (2C), 128.3, 124.9, 123.8, 123.7, 122.0, 121.2, 112.1, 112.0, 53.5, 53.1, 39.2, 31.3, 21.5. IR ( $\mathrm{V}_{\text {max }} \mathrm{cm}^{-1}$ ) 2954 (w), 1728 (s), 1678 (m), 1443 (m), 1386 (m), 1274 (s), 1197 (s), $1130(\mathrm{~m}), 914(\mathrm{w})$. HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{16} \mathrm{NaO}_{6}{ }^{+}$375.0839; Found 375.0839.


Following a reported procedure, ${ }^{12}$ acrylophenone was added to a solution of methyl dichloroacetate ( $1.04 \mathrm{~mL}, 10.0 \mathrm{mmol}, 1.0$ equiv.) and $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ ( $3.58 \mathrm{~g}, 11.0 \mathrm{mmol}, 1.1$ equiv.) in 20 mL of DMF , the mixture was stirred at room temperature and monitored by TLC analysis until full conversion of acrylophenone. Upon completion, water ( 10 mL ) was added to mixture and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( $3 x$ $20 \mathrm{ml})$. The combined organic layers were dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated under reduced pressure. The residue was purified by chromatography on Biotage (Gradient ethyl acetate:pentanes from 1:20 to 1:8) to provide the corresponding cyclopropanes $1 \mathrm{v}(1.46 \mathrm{~g}, 6.10 \mathrm{mmol}$, $61 \%$ yield over 2 steps) as white solid. The ratio was determined in the isolated mixture using the signal of $\mathrm{CHCH}_{2} 2.25$ (major), 2.43 ppm (minor) (dr: 88:12). The NMR data is reported for the major diastereoisomer only.

TLC: $\mathrm{R}_{\mathrm{f}}=0.37\left(\mathrm{SiO}_{2}\right.$, pentane:EA 90:10). MP : 58-62 ${ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.00-7.96(\mathrm{~m}$, 2H, ArH), 7.64-7.59 (m, 1H, ArH), 7.54-7.48 (m, 2H, ArH), $3.90\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.55(\mathrm{dd}, \mathrm{J}=9.1,7.9$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.25 (dd, $J=7.9,5.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $2.00\left(\mathrm{dd}, J=9.1,5.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR (101 MHz, CDCl $_{3}$ ) $\delta 191.7,169.6,137.1,133.9,129.0,128.7,54.2,43.6,33.7,22.3$. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-}$ ${ }^{1}$ ) 2953 (w), 1750 (m), 1728 (s), 1685 (s), 1595 (w), 1375 (m), 1281 (s), 1224 (s), 1134 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{12} \mathrm{H}_{11} \mathrm{ClNaO}_{3}{ }^{+}$261.0289; Found 261.0285 .

## Methyl 2-benzoyl-1-fluorocyclopropane-1-carboxylate (1w)



Following a reported procedure, ${ }^{13}$ to a solution of $\mathbf{1 v}$ ( $238 \mathrm{mg}, 1.00 \mathrm{mmol}, 1.00$ equiv.) in DMSO ( 2 mL ), was added $\mathrm{KHF}_{2}$ ( $234 \mathrm{mg}, 3.00 \mathrm{mmol}, 3.0$ equiv.) and the mixture was stirred at $120^{\circ} \mathrm{C}$ until full conversion of $\mathbf{1 v}$ as indicated by TLC analysis. 2 mL of water was then added to the mixture and it was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 5 \mathrm{~mL})$. The combined organic layers were dried with anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated under reduced pressure. The residue was purified by chromatography on Biotage (Gradient ethyl acetate/pentanes from 1:20 to 1:8) to provide the corresponding cyclopropanes 1w (162 $\mathrm{mg}, 0.730 \mathrm{mmol}, 73 \%$ yield) as colorless oil. The ratio was determined in the isolated mixture using the signal of $\mathrm{C}(\mathrm{O}) \mathrm{CH} 3.46$ (major), 3.19 ppm (minor) (dr: 68:32). The NMR data is reported for the major diastereoisomer only.

TLC: $\mathrm{R}_{\mathrm{f}}=0.25\left(\mathrm{SiO}_{2}\right.$, pentane:EA 90:10). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.04-7.96(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.67-$ $7.58(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.55-7.45(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}$ ), 3.46 (ddd, $J=9.4,8.2,3.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.48$ (ddd, J $\left.=18.6,8.2,6.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.83\left(\mathrm{td}, J=9.3,6.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C} \mathbf{N M R}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ $190.5,169.2$ (d, $J=24.2 \mathrm{~Hz}$ ), 137.3, 133.8, 128.9, 128.6, 78.9 (d, $J=245.3 \mathrm{~Hz}), 53.4,31.4$ (d, $J=11.2$ Hz ), $18.0(\mathrm{~d}, \mathrm{~J}=10.4 \mathrm{~Hz}) .{ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-206.2$ (ddd, $J=18.4,9.3,2.8 \mathrm{~Hz}$ ). IR ( $\mathrm{v}_{\mathrm{max}}$, $\mathrm{cm}^{-1}$ ) 2959 ( w ), 1752 (s), 1684 (s), 1598 (w), 1447 (m), 1388 (m), 1306 (s), 1224 (s), 1159 (s). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{12} \mathrm{H}_{11} \mathrm{FNaO}_{3}{ }^{+}$245.0584; Found 245.0584.

## Methyl 2-benzoyl-1-(((13S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)cyclopropane-1-carboxylate (1x)



Following a reported procedure, ${ }^{12}$ the mixture of $\mathbf{1 v}$ ( $238 \mathrm{mg}, 1.00 \mathrm{mmol}, 1.0$ equiv.), estrone ( 270 mg , $1.00 \mathrm{mmol}, 1.0$ equiv.) and $\mathrm{Cs}_{2} \mathrm{CO}_{3}\left(717 \mathrm{mg}, 2.20 \mathrm{mmol}, 2.2\right.$ equiv.) in 4 mL of $\mathrm{CH}_{3} \mathrm{CN}$ was stirred at room temperature overnight. The reaction was monitored by TLC until full conversion of $\mathbf{1 v} .4 \mathrm{~mL}$ of water was added and the mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 5 \mathrm{~mL})$. The combined organic layers were dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated under reduced pressure. The residue was purified by chromatography on Biotage (Gradient ethyl acetate:pentanes from 1:20 to 1:4) to provide the corresponding cyclopropanes $\mathbf{1 x}(198 \mathrm{mg}, 0.419 \mathrm{mmol}, 42 \%)$ as sticky oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.40\left(\mathrm{SiO}_{2}\right.$, pentane:EA $\left.70: 30\right) .{ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.95(\mathrm{td}, J=8.6,1.3 \mathrm{~Hz}, 2 \mathrm{H}$, ArH), $7.61-7.56$ (m, 1H, ArH), 7.47 (td, $J=7.7,3.7 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $7.10-7.05(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.61 (dd, J $=8.6,2.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.51 (dd, $J=17.2,2.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 3.84 (d, J=1.0 Hz, 3H, OCH3), 3.64 (dt, $J=9.0,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.85-2.61 (m, 2H, H-estrone ), 2.49 (dd, $J=19.1,8.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}$ ), 2.36-2.24 (m, 2H, H-estrone), 2.22-2.09 (m, 2H, H-estrone), 2.02 (ddt, J=14.4, 9.0, 2.9 Hz, 2H, CHCH2 and $H$-estrone), 1.93 (ddd, $J=12.2,6.5,2.5 \mathrm{~Hz}, 2 \mathrm{H}, H$-estrone), 1.61 (dt, $J=12.4,9.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}$ estrone), 1.54-1.42 (m, 4H, $H$-estrone), 1.34 (ddq, $J=30.0,12.0,6.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}$-estrone), 0.89 (d, $J=$ $3.3 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}$ ).
${ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 221.1,191.5(\mathrm{~d}, J=3.0 \mathrm{~Hz}), 171.5(\mathrm{~d}, J=3.0 \mathrm{~Hz}), 155.2(\mathrm{~d}, J=2.5 \mathrm{~Hz})$, $137.8(\mathrm{~d}, J=2.1 \mathrm{~Hz}), 137.8,137.8,133.5(\mathrm{~d}, J=7.6 \mathrm{~Hz}), 133.3(\mathrm{~d}, J=4.2 \mathrm{~Hz}), 128.7(\mathrm{~d}, J=2.5 \mathrm{~Hz})$, $128.5(\mathrm{~d}, J=4.6 \mathrm{~Hz}), 126.3(\mathrm{~d}, J=8.6 \mathrm{~Hz}), 115.9(\mathrm{~d}, J=28.0 \mathrm{~Hz}), 113.0(\mathrm{~d}, J=41.8 \mathrm{~Hz}), 63.8(\mathrm{~d}, J=$ $4.7 \mathrm{~Hz}), 53.4,50.5,48.1,44.1(\mathrm{~d}, J=5.7 \mathrm{~Hz}), 38.3,36.0,34.0(\mathrm{~d}, J=2.5 \mathrm{~Hz}), 31.7,29.6$ (d, $J=3.6 \mathrm{~Hz})$, 26.6 (d, J=3.5 Hz), 25.9 (d, J=8.3 Hz), 21.7, 20.3 (d, J=3.6 Hz), 14.0. IR ( $\mathrm{v}_{\mathrm{max}}, \mathrm{cm}^{-1}$ ) 2935 (w), 2366 (w), 1734 (m), 1682 (w), 1494 (w), 1299 (m), 1224 (m), 1155 (m), 910 (s), 907 (s). HRMS (ESI/QTOF) $\mathrm{m} / \mathrm{z}:[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{30} \mathrm{H}_{32} \mathrm{NaO}_{5}{ }^{+} 495.2142$; Found 495.2141
(2-(((3-(Naphthalen-1-yl)prop-2-yn-1-yl)oxy)methyl)cyclopropyl)(phenyl)methanone (6a)


Following slightly modified reported procedure, ${ }^{10 \mathrm{~b}}$ a solution of 1-bromo-3-butene $\mathbf{S 1 9}$ ( $1.22 \mathrm{~mL}, 10.0$ $\mathrm{mmol}, 1.0$ equiv. in THF 10 mL ) was added dropwise to a flask containing Magnesium turnings ( 14.0 $\mathrm{mmol}, 346 \mathrm{mg}, 1.2$ equiv.) suspended in THF ( 10 mL ). The reaction was stirred for 30 minutes. The reaction mixture was then cooled to $0^{\circ} \mathrm{C}$ before a solution of Weinreb amide $\mathbf{S 1 8}(10 \mathrm{mmol}, 0.1 \mathrm{M}, 1.0$ equiv. in THF) was added dropwise. The reaction was stirred overnight, the temperature was slowly increased to rt. After that, the reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic layers were dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated under reduced pressure. The residue was directly dissolved in DMSO ( 30 ml ) containing 0.5 mL water. NBS ( $2.2 \mathrm{~g}, 12 \mathrm{mmol}, 1.1$ equiv.) was added and the solution was stirred for 15 minutes. $\mathrm{KOH}(3.1 \mathrm{~g}, 55$
mmol, 5.0 equiv.) was then added and the mixture was stirred at room temperature overnight. The reaction mixture was then neutralized with $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic layers were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated under reduced pressure. The residue ( $\mathbf{S 2 1}$ ) was directly used for the next step without further purification.

A quarter of crude mixture S21 prepared above (approximate 2 mmol ) in DMF ( 2 mL ) was added dropwise to a suspension of $\mathrm{NaH}(96.0 \mathrm{mg}, 2.40 \mathrm{mmol}, 60 \mathrm{wt} \%$ in mineral oil, 1.2 equiv.) in anhydrous DMF ( 25 mL ) at $0{ }^{\circ} \mathrm{C}$ under $\mathrm{N}_{2}$. The resulting mixture was stirred at $0^{\circ} \mathrm{C}$ for 30 min . After that, ( $3-$ bromoprop-1-yn-1-yl)naphthalene $\mathbf{S 2 2}$ ( $0.468 \mathrm{~g}, 2.40 \mathrm{mmol}, 1.2$ equiv.) was slowly added to the mixture, the solution was stirred overnight and gradually warmed up to room temperature. After that, the resulting solution was quenched with sat. $\mathrm{NH}_{4} \mathrm{Cl}(10 \mathrm{~mL})$, and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 10 \mathrm{~mL})$. The organic layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated under reduced pressure. The residue was purified by Biotage (Büchi flash pure cartridge 40 g , gradient of pentane: diethyl ether from 100:0 to $85: 15$ ) to afford the desire product $\mathbf{6 a}(242 \mathrm{mg}, 0.711 \mathrm{mmol}, 36 \%$ yield for 3 steps) as a yellow oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl $)_{3}$ ) 8.34 - 8.29 (m, 1H, ArH), 8.08 - $8.00(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.89-7.82(\mathrm{~m}, 2 \mathrm{H}$, ArH), $7.69(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 7.59-7.50(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH}), 7.47-7.38(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH}), 4.58(\mathrm{~s}, 2 \mathrm{H}$, $\mathrm{OCH}_{2}$ ), 3.88 (dd, $J=10.5,5.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}$ ), 3.64 (dd, $J=10.4,7.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}$ ), $2.75-2.71$ ( m , $1 \mathrm{H}, \operatorname{ArCOCH}$ ), $2.05-1.96\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}\right), 1.56-1.52\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.16-1.11\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.5,138.0,133.5,133.3,132.9,130.9,129.2,128.7,128.5,128.3,127.0$, 126.6, 126.2, 125.3, 120.3, 90.0, 84.7, 71.6, 58.8, 24.8, 23.2, 15.9. HRMS (ESI/QTOF) m/z: [M + $\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{20} \mathrm{NaO}_{2}{ }^{+} 363.1356$; Found 363.1360 . Data matching reported value. ${ }^{10 \mathrm{~b}}$

## (2-((Cinnamyloxy)methyl)cyclopropyl)(phenyl)methanone (6b)



Starting from a quarter of crude mixture $\mathbf{S 2 1}$ prepared above (approximate 2 mmol ) in DMF ( 2 mL ) and 3-bromo-1-phenyl-1-propene ( $0.473 \mathrm{~g}, 2.40 \mathrm{mmol}, 1.2$ equiv.) was used for final etherification. (The residue was purified by Biotage (Büchi flash pure cartridge 40 g , gradient of pentane: diethyl ether from 100:0 to $80: 20$ ) to afford the desire product $\mathbf{6 b}(239 \mathrm{mg}, 0.820 \mathrm{mmol}, 41 \%$ yield after three steps) as a yellow oil. TLC: $\mathrm{R}_{\mathrm{f}}=0.31\left(\mathrm{SiO}_{2}, 5: 1\right.$ Pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.04-7.94(\mathrm{~m}$, 2H, ArH), $7.55-7.48$ (m, 1H, ArH), $7.44-7.38$ (m, 2H, ArH), $7.36-7.30$ (m, 2H, ArH), $7.29-7.23$ (m, 2H, ArH), 7.22 - 7.19 (m, 1H, ArH), $6.61-6.51$ (m, 1H, ArCH), 6.24 (dt, J= 15.9, 6.0 Hz, 1H, ArCHCH), 4.13 (dt, $J=6.0,1.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArCHCHCH}_{2} \mathrm{O}$ ), 3.60 (dd, $J=10.5,5.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{OCH}_{2}$ ), 3.41 (dd, $J=$ $10.5,6.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{OCH}_{2}$ ), 2.62 (dt, $J=8.4,4.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), $1.96-1.85(\mathrm{~m}, 1 \mathrm{H}, \mathrm{COCHCH}$ ), 1.48 (ddd, $J=8.7,4.9,3.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{COCHCH}_{2}$ ), 1.03 (ddd, $J=8.0,6.3,3.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{COCHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 199.5,138.1,136.7,132.9,132.6,128.7,128.6,128.3,127.9,126.6,126.1$, 72.0, 71.3, 25.2, 23.2, 15.9. IR ( $\mathrm{v}_{\mathrm{max}} \mathrm{cm}^{-1}$ ) 3026 (m), 2857 (m), 1674 (s), 1664 (s), 1659 (s), 1449 (s), 1360 (s), 1222 (s), 1112 (s), 1076 (s), 967 (s). HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for $\mathrm{C}_{20} \mathrm{H}_{20} \mathrm{NaO}_{2}{ }^{+} 315.1356$; Found 315.1358.

## Cyclobutane-1,2-diyl)bis(phenylmethanone) (8)




A solution of $(\mathrm{COCl})_{2}(4.0 \mathrm{~mL}, 47 \mathrm{mmol})$ in DCM $(10 \mathrm{~mL})$ was added dropwise at room temperature, under nitrogen, to a solution of trans-cyclobutane-1,2-dicarboxylic acid ( $720 \mathrm{mg}, 5.00 \mathrm{mmol}, 1.0$ equiv.) in 10 ml of $\mathrm{DCM}+0.5 \mathrm{ml}$ DMF. The mixture was stirred overnight at room temperature, then the solvent was removed under vacuum. The mixture was then dissolved in benzene ( 10 mL ) and the solution was cooled down to $0{ }^{\circ} \mathrm{C} . \mathrm{AlCl}_{3}(1.33 \mathrm{~g}, 10.0 \mathrm{mmol}, 2.0$ equiv.) was added portions wise. The reaction was stirred overnight and the temperature was gradually increased to room temperature. The resulted mixture was quenched with water at $0{ }^{\circ} \mathrm{C}$ then extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 20 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated under reduced pressure. The residue was purified by Biotage (Büchi flash pure cartridge 40 g , gradient of pentane: diethyl ether from 100:0 to $95: 5$ ) to afford the desire product. The product was further re-crystallized with DCM/Pentane (3/1) to obtain final product 8 as a white solid ( $726 \mathrm{mg}, 2.75 \mathrm{mmol}, 55 \%$ yield). TLC: $\mathrm{R}_{\mathrm{f}}=0.43\left(\mathrm{SiO}_{2}, 5: 1\right.$ Pentane: $\mathrm{Et}_{2} \mathrm{O}$ ). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) б $8.00-7.91$ (m, 4H, ArH), $7.59-7.48$ (m, 2H, ArH), 7.51 - 7.40 (m, 4H, ArH), 4.55 (ddd, J= 8.7, 6.3, $2.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArCOCH}$ ), 2.37 (dtd, $\left.J=10.6,5.6,2.1 \mathrm{~Hz}, 4 \mathrm{H}, \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.8$, 135.3, 133.4, 128.8, 128.7, 42.4, 23.0. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 3063 (w), 2946 (w), 1679 (s), 1671 (s), 1597 (m), 1448 (m), 1322 (m), 1223 (s), 1180 (m), 1023 (m). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{16} \mathrm{NaO}_{2}{ }^{+}$287.1043; Found 287.1050.

Alkynes and olefin reagents are commercially available and were used as received without further purification








3a
3b
3c
3d
3e
3f
3g
3h
$3 i$

5a






## Synthesis of Bicyclo[1.1.0]butanes




Following a reported procedure, ${ }^{14}$ a solution of 3-oxocyclobutane carboxylic acid $\mathbf{S 2 3}$ (1.0 equiv.) in anhydrous THF ( 0.50 M ) in an oven-dried flask was cooled to $0^{\circ} \mathrm{C}$ under nitrogen atmosphere. Then the Grignard reagent ( 2.0 equiv.) was added dropwise. After the addition, the solution was allowed to warm to room temperature and stirred overnight. The mixture was then quenched with excess 1 M HCl solution at $0^{\circ} \mathrm{C}$. The mixture was then extracted with EtOAc ( 3 times), and the combined organic layers were then washed with saturated $\mathrm{NaHCO}_{3}$ solution (2 times). The combined aqueous layers were then acidified to $\mathrm{pH}<3$ and extracted with ethyl acetate 2 times. All combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford the corresponding crude 3-oxy-3arylcyclobutane carboxylic acid $\mathbf{S} \mathbf{2 6}$ which was added to the next step without further purification.

If starting from aryl bromide (S24). A solution of n-butyl lithium (2.0 equiv.) was slowly added to a solution of the aryl bromide $\mathbf{S 2 4}$ ( 2.0 equiv.) in anhydrous THF ( 0.50 M ) under nitrogen atmosphere at $-78{ }^{\circ} \mathrm{C}$. The reaction was stirred at this temperature for two hours. After that, a solution of 3oxocyclobutane carboxylic acid (S25, 1.0 equiv.) in THF ( 1 M ) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The quenching step and extraction followed the same as protocol mentioned with the Grignard reagent.

S26 was added to a round-bottom flask. Toluene ( 0.50 M starting material) and concentrated HCl solution ( $37 \%, 1.00 \mathrm{M}$ starting material) were added and the mixture was stirred vigorously at room temperature overnight. The mixture was transferred to extraction funnel and the aqueous layer was extracted with EtOAc (2 times). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum to afford the crude 3-chloro-3-arylcyclobutane carboxylic acid S27.

Potassium carbonate ( 2.0 equiv.) was added to a solution of this material ( $\mathbf{S 2 7}, 1.0$ equiv.) in DMF ( 0.50 M), followed by slowly addition of methyl iodide ( 2.0 equiv.). The mixture was stirred at room temperature overnight. A solution of $5 \%$ lithium chloride was added to the reaction and the mixture was extracted with ethyl acetate ( 3 times). The combined organic layers were washed with brine and dried over sodium sulfate. The mixture was filtered, concentrated under reduced pressure, to afford the crude of the corresponding 3-chloro-3-arylcyclobutane S28.

The solution of the crude mixture $\mathbf{S 2 8}$ ( 1.0 equiv.) in toluene ( 0.50 M ) was cooled to $0^{\circ} \mathrm{C}$ and NaHMDS (2.0 M in THF, 1.2 equiv.) was added slowly. The reaction was then stirred at $0^{\circ} \mathrm{C}$ for 30 minutes and for two hours at room temperature. After this time, a saturated ammonium chloride solution was added slowly to quench the reaction. The mixture was then extracted with diethyl ether (3 times), and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on Biotage (Büchi flashpure cartridge 40 g , gradient of pentane:ethyl acetate from 100:0 to 95:5) to afford corresponding BCBs (11a-i).

## Methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate (11a)



Following general procedure D, using 3-oxocyclobutane carboxylic acid (S23, $1.41 \mathrm{~g}, 10.0 \mathrm{mmol}, 1.0$ equiv.), phenylmagnesium bromide solution ( 1.00 M in THF, $20.0 \mathrm{~mL}, 20.0 \mathrm{mmol}, 2.0$ equiv.), iodomethane ( $1.25 \mathrm{~mL}, 20.0 \mathrm{mmol}, 2.0$ equiv.) and potassium carbonate ( $2.76 \mathrm{~g}, 20.0 \mathrm{mmol}, 2.0$ equiv.), NaHMDS solution ( 1.00 M in THF, $12.0 \mathrm{~mL}, 12.0 \mathrm{mmol}$, 1.2 equiv.) afforded the desired compound 11a ( $809 \mathrm{mg}, 4.30 \mathrm{mmol}, 43 \%$ over 4 steps) as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) б 7.36-7.27 (m, 3H, ArH), 7.24-7.20 (m, 2H, ArH), $3.50\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.90$ (s, 2H, CH2), $1.62\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right)$. Data matching reported values. ${ }^{14}$
Methyl 3-(2-fluorophenyl)bicyclo[1.1.0]butane-1-carboxylate (11b)


Following general procedure D, using 3-oxocyclobutane carboxylic acid ( $\mathbf{S 2 3}, 2.28 \mathrm{~g}, 20.0 \mathrm{mmol}, 1.0$ equiv.), 1-bromo-2-fluorobenzene ( $4.59 \mathrm{~mL}, 42.0 \mathrm{mmol}, 2.1$ equiv.), $n$-butyllithium solution ( 2.50 M in hexanes, $16.8 \mathrm{~mL}, 42.0 \mathrm{mmol}, 2.1$ equiv.), iodomethane ( $2.49 \mathrm{~mL}, 40.0 \mathrm{mmol}, 2.0$ equiv.), potassium carbonate ( $5.53 \mathrm{~g}, 40.0 \mathrm{mmol}, 2.0$ equiv.) and NaHMDS solution ( $1.00 \mathrm{M} \mathrm{in} \mathrm{THF} 24.0 \mathrm{~mL},, 24.0 \mathrm{mmol}$, 1.2 equiv.) afforded the desired compound $\mathbf{1 1 b}$ ( $2.06 \mathrm{~g}, 10.0 \mathrm{mmol}, 50 \%$ over 4 steps) as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.29-7.16(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.10-6.98(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 3.59\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $2.91\left(\mathrm{q}, J=1.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.61\left(\mathrm{q}, J=1.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right)$. Data matching reported values. ${ }^{14}$

## Methyl 3-(4-chlorophenyl)bicyclo[1.1.0]butane-1-carboxylate (11c)



Following general procedure D, using 3-oxocyclobutane carboxylic acid (S23, $1.43 \mathrm{~g}, 12.5 \mathrm{mmol}, 1.0$ equiv.), a (4-chlorophenyl)magnesium bromide solution ( 1.00 M in $2-\mathrm{Me}$ THF, $25.0 \mathrm{~mL}, 25.0 \mathrm{mmol}, 2.0$ equiv.), iodomethane ( $1.56 \mathrm{~mL}, 25.0 \mathrm{mmol}, 2.0$ equiv.) and potassium carbonate ( $3.45 \mathrm{~g}, 25.0 \mathrm{mmol}$, 2.0 equiv.). The corresponding crude 3 -chloro-3-arylcyclobutane ( $1.58 \mathrm{~g}, 6.11 \mathrm{mmol}, 1.0$ equiv.) was converted to the desired product using a solution of NaHMDS ( 1.00 M in THF, $7.33 \mathrm{~mL}, 7.33 \mathrm{mmol}, 1.2$ equiv.) to afford the desired compound $\mathbf{1 1 c}(1.42 \mathrm{~g}, 6.37 \mathrm{mmol}, 51 \%$ over 4 steps $)$ as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.32-7.29(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.24-7.19(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 3.50\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $2.89\left(\mathrm{t}, \mathrm{J}=1.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.62\left(\mathrm{t}, \mathrm{J}=1.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right)$. Data matching reported values. ${ }^{14}$

## Methyl 3-(4-(trifluoromethyl)phenyl)bicyclo[1.1.0]butane-1-carboxylate (11d)



Following general procedure D, using 3-oxocyclobutane carboxylic acid ( $\mathbf{S 2 3}, 2.28 \mathrm{~g}, 20.0 \mathrm{mmol}, 1.0$ equiv.), 1-bromo-4-(trifluoromethyl)benzene ( $5.60 \mathrm{~mL}, 40.0 \mathrm{mmol}, 2.0$ equiv.), a $n$-butyllithium solution ( 2.50 M in hexanes, $22.8 \mathrm{~mL}, 57.0 \mathrm{mmol}, 2.85$ equiv.), iodomethane ( $2.49 \mathrm{~mL}, 40.0 \mathrm{mmol}, 2.0$ equiv.), potassium carbonate ( $5.53 \mathrm{~g}, 40.0 \mathrm{mmol}, 2.0$ equiv.) and a NaHMDS solution ( 1.00 M in THF, 24.0 mL , 1.2 equiv.) afforded the desired compound 11 d ( $1.79 \mathrm{~g}, 7.00 \mathrm{mmol}, 35 \%$ over 4 steps ) as a pale yellow solid.
${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.58-7.52(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.41-7.36(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 3.50\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $2.95\left(\mathrm{t}, \mathrm{J}=1.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.66(\mathrm{t}, \mathrm{J}=1.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH})_{2}$. Data matching reported values. ${ }^{14}$

## Methyl 3-(4-(methoxycarbonyl)phenyl)bicyclo[1.1.0]butane-1-carboxylate (11e)



This compound was synthesized using a modified general procedure D for the first step. An isopropyl magnesium chloride lithium complex solution ( 1.30 M in THF, 13.5 mL , $17.6 \mathrm{mmol}, 2.2$ equiv.) was added dropwise to a solution of methyl 4 -iodobenzoate ( $4.61 \mathrm{~g}, 17.6 \mathrm{mmol}, 2.2$ equiv.) in anhydrous THF ( 16.0 mL ) under inert atmosphere at $-78^{\circ} \mathrm{C}$ and the reaction was stirred at this temperature for 30 minutes. Then, a 3 -oxocyclobutane carboxylic acid ( $\mathbf{S 2 3}, 913 \mathrm{mg}, 8.00 \mathrm{mmol}, 1.0$ equiv.) solution in anhydrous THF ( 10.0 mL ) was added dropwise to the reaction mixture. The next step followed general procedure D, iodomethane ( $2.19 \mathrm{~mL}, 35.20 \mathrm{mmol}, 2.0$ equiv.), potassium carbonate ( $5.53 \mathrm{~g}, 40.0 \mathrm{mmol}$, 2.27 equiv.) and a NaHMDS solution ( 1.00 M in THF, $24.0 \mathrm{~mL}, 1.36$ equiv.) to afford the title compound 11e ( $562 \mathrm{mg}, 2.28 \mathrm{mmol}, 28 \%$ over 4 steps) as white fluffy crystals.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.04-7.82(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.40-7.28(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 3.90\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.48$ (s, 3H, OCH ${ }_{3}$ ), $2.97\left(\mathrm{t}, \mathrm{J}=1.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.67\left(\mathrm{t}, \mathrm{J}=1.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right)$. Data matching reported values. ${ }^{14}$

## Methyl 3-(4-(trifluoromethoxy)phenyl)bicyclo[1.1.0]butane-1-carboxylate (11f)



Following general procedure D, using 3-oxocyclobutane carboxylic acid (S23, $1.71 \mathrm{~g}, 15.0 \mathrm{mmol}, 1.0$ equiv.), 1-bromo-4-(trifluoromethoxy)benzene ( $4.46 \mathrm{~mL}, 30.0 \mathrm{mmol}, 2.0$ equiv.), a $n$-butyllithium solution
( 2.50 M in hexanes, $12.0 \mathrm{~mL}, 30.0 \mathrm{mmol}, 2.0$ equiv.), iodomethane ( $1.40 \mathrm{~mL}, 22.5 \mathrm{mmol}, 1.5$ equiv.), potassium carbonate ( $4.15 \mathrm{~g}, 30.0 \mathrm{mmol}, 2.0$ equiv.) and NaHMDS ( 1.00 M in THF, $18.0 \mathrm{~mL}, 18.0$ mmol, 1.2 equiv.) afforded the desired compound $11 \mathrm{f}(1.71 \mathrm{~g}, 6.30 \mathrm{mmol}, 42 \%$ over 4 steps) as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.33-7.28(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.17-7.12(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 3.50\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.90$ ( $\mathrm{t}, \mathrm{J}=1.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}$ ) , $1.63\left(\mathrm{t}, \mathrm{J}=1.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right.$ ). Data matching reported values. ${ }^{14}$

## Methyl 3-(3-methoxyphenyl)bicyclo[1.1.0]butane-1-carboxylate (11g):



Following general procedure D, using 3-oxocyclobutane carboxylic acid (S23, $2.28 \mathrm{~g}, 20.0 \mathrm{mmol}, 1.0$ equiv.), 1-iodo-3-methoxybenzene ( $4.76 \mathrm{~mL}, 40.0 \mathrm{mmol}, 2.0$ equiv.), a $n$-butyllithium solution ( 2.50 M in hexanes, $22.8 \mathrm{~mL}, 57.0 \mathrm{mmol}$, 2.85 equiv.), the corresponding crude 3 -chloro- 3 -arylcyclobutane carboxylic acid ( $\mathbf{S 3}, 1.58 \mathrm{~g}, 6.58 \mathrm{mmol}$ ) was converted into the desired product using iodomethane ( $0.82 \mathrm{~mL}, 13 \mathrm{mmol}, 2.0$ equiv.), potassium carbonate ( $1.82 \mathrm{~g}, 13.2 \mathrm{mmol}, 2.0$ equiv.) and a NaHMDS solution ( 1.00 M in THF, $7.90 \mathrm{~mL}, 7.90 \mathrm{mmol} 1.2$ equiv.) to afford the desired compound $\mathbf{1 1 g}$ ( 436 mg , $2.00 \mathrm{mmol}, 10 \%$ over 4 steps) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.21(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.89 (ddd, $J=7.7,1.7,1.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.83 (t, $J=2.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.77 (ddd, $J=8.2,2.6,1.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), $3.80\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), 3.51 ( $\mathrm{s}, 3 \mathrm{H}$, $\left.\mathrm{OCH}_{3}\right), 2.91\left(\mathrm{t}, J=1.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.59\left(\mathrm{t}, J=1.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right)$. Data matching reported values. ${ }^{15}$

## Methyl 3-(m-tolyl)bicyclo[1.1.0]butane-1-carboxylate (11h):



Following general procedure D, using 3-oxocyclobutane carboxylic acid (S23, $1.14 \mathrm{~g}, 10.0 \mathrm{mmol}, 1.0$ equiv.), 1-bromo-3-methylbenzene ( $2.43 \mathrm{~mL}, 20.0 \mathrm{mmol}, 2.0$ equiv.), a $n$-butyllithium solution ( 2.50 M in hexanes, $8.00 \mathrm{~mL}, 20.0 \mathrm{mmol}, 2.0$ equiv.), iodomethane ( $0.93 \mathrm{~mL}, 15.0 \mathrm{mmol}, 1.5$ equiv.), potassium carbonate ( $2.76 \mathrm{~g}, 20.0 \mathrm{mmol}, 2.0$ equiv.) and a NaHMDS solution ( 1.00 M in THF, $11.0 \mathrm{~mL}, 11.0 \mathrm{mmol}$, 1.1 equiv.) afforded the desired compound $\mathbf{1 1 h}(627 \mathrm{mg}, 3.10 \mathrm{mmol}, 31 \%$ over 4 steps ) as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.18$ (t, $J=7.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.12-7.02 (m, 3H, ArH), $3.50\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $2.90\left(\mathrm{t}, J=1.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.32\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{ArCH}_{3}\right), 1.58\left(\mathrm{t}, J=1.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right)$. Data matching reported values. ${ }^{15}$


Following general procedure D, using 3-oxocyclobutane carboxylic acid (S28, $1.43 \mathrm{~g}, 12.5 \mathrm{mmol}, 1.0$ equiv.) and a ( 4 -chlorophenyl)magnesium bromide solution ( 1.00 M in 2-Me THF, $25.0 \mathrm{~mL}, 25.0 \mathrm{mmol}$, 2.0 equiv.), the crude 3-chloro-3-arylcyclobutane carboxylic acid ( $\mathbf{S 3}, 1.23 \mathrm{~g}$, nominally $5.00 \mathrm{mmol}, 1.0$ equiv.) was converted to the desired product using allyl iodide ( $0.91 \mathrm{~mL}, 10 \mathrm{mmol}, 2.0$ equiv.), potassium carbonate ( $1.38 \mathrm{~g}, 10.0 \mathrm{mmol}$, 2.0 equiv.), and a NaHMDS solution ( 1.00 M in THF, 6.00 $\mathrm{mL}, 6.00 \mathrm{mmol}, 1.2$ equiv.) to afford the desired compound $11 \mathrm{i}(186 \mathrm{mg}, 0.750 \mathrm{mmol}, 15 \%$ over two steps) as a colorless oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.37\left(\mathrm{SiO}_{2}\right.$, pentane:EtOAc 95:5). ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ ס $7.24-7.20(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.17-$ 7.14 (m, 2H, ArH), 5.55 (ddt, $J=17.0,10.6,5.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH} 2=\mathrm{CH}$ ), $5.04-4.91\left(\mathrm{~m}, 2 \mathrm{H} \mathrm{CH} 2 \mathrm{CH}=\mathrm{CH}_{2}\right)$, $4.33\left(\mathrm{dt}, J=5.7,1.4 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{OCH}_{2} \mathrm{CH}\right), 2.86\left(\mathrm{t}, \mathrm{J}=1.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CCH}_{2}\right), 1.57\left(\mathrm{t}, J=1.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CCH}_{2}\right.$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 169.2,132.3,128.8,128.8,127.4,126.2,117.9,65.4,36.1,32.5,29.9$, 23.6. HRMS (APPI/LTQ-Orbitrap) m/z: [M] ${ }^{+}$Calcd for $\mathrm{C}_{14} \mathrm{H}_{13} \mathrm{ClO}_{2}{ }^{+}$248.0599; Found 248.0606. IR ( $\mathrm{v}_{\mathrm{max}}$, $\left.\mathrm{cm}^{-1}\right) 2928$ (m), 2859 (w), 1711 (s), 1487 (m), 1415 (m), 1339 (m), 1159 (s), 1094 (m), 915 (m).

## Optimization table and control experiments

In a 12*75 mm borosilicate glass tube was added the photocatalyst ( $1.0 \mathrm{~mol} \%$ ) and the cyclopropane (if as a solid). The tube was closed with a rubber septum and sealed off with parafilm. Three cycles of evacuate-refill with nitrogen were performed to remove $\mathrm{O}_{2}$ and extra-dry solvent in a sealed-cap bottle of Acros was added ( 0.10 M ) under nitrogen atmosphere. Cyclopropane $(0.10 \mathrm{mmol}, 1.0$ equiv., if as a liquid), alkyne or olefin were also added at this stage. The reaction mixture was stirred at room temperature for indicated time under irradiation with a Kessil lamp 440 nm . A flow of compressed air was used for cooling purposes or a fan on top of a stirring plate. Upon completion, the mixture was concentrated in vacuo and purified by flash column chromatography (pentane:diethyl ether) for purification or biotage with gradient of pentane:diethyl ether. NMR yield was determined by adding 1.0 equiv. of benzylbenzoate as internal standard, ArCOCH signal was used to determine the NMR yield.

## Table S1



In a $12^{\star} 75 \mathrm{~mm}$ borosilicate glass tube was added the photocatalyst ( $1.0 \mathrm{~mol} \%$ ), cyclopropane ( 0.10 $\mathrm{mmol}, 1.0$ equiv., if as a solid), ( PhO ) $\mathrm{PO}_{2} \mathrm{H}$ and BCBs . The tube was closed with a rubber septum and sealed off with parafilm. Three cycles of evacuate-refill with nitrogen were performed to remove $\mathrm{O}_{2}$ and extra-dry solvent in a sealed-cap bottle of Acros was added ( 0.10 M ) under nitrogen atmosphere. The cyclopropane ( $0.10 \mathrm{mmol}, 1.0$ equiv., if as a liquid) was also added at this stage. The reaction mixture was stirred at room temperature for the indicated time under irradiation with a Kessil lamp 440 nm . A flow of compressed air was used for cooling purposes or a fan on top of a stirring plate. Upon completion, the mixture was concentrated in vacuo and purified by flash column chromatography (pentane:diethyl ether) for purification or biotage with gradient of pentane:diethyl ether. NMR yield was determined by adding 1.0 equiv. of benzylbenzoate as internal standard, ArCOCH signal was used to determine the NMR yield.

Table S2


## Synthesis of $[2 \sigma+2 \pi]$ products.

## General procedure E.

In a $12^{*} 75 \mathrm{~mm}$ borosilicate glass tube were added the photocatalyst ( $1.0 \mathrm{~mol} \%$ ) and the cyclopropane ( 1.0 equiv., if as a solid). The tube was closed with a rubber septum and sealed off with parafilm. Three cycles of evacuate-refill with nitrogen were performed to remove $\mathrm{O}_{2}$ and extra-dry solvent in a sealedcap bottle of Acros was added ( 0.10 M ) under nitrogen atmosphere. The cyclopropane ( $0.20 \mathrm{mmol}, 1.0$ equiv., if as a liquid), the alkyne (1.5-5.0 equiv.) or the olefin ( 1.5 equiv.) were also added at this stage. The reaction mixture was stirred at room temperature for indicated time under irradiation with a Kessil lamp 440 nm . A flow of compressed air was used for cooling purposes or a fan on top of stirring plate. Upon completion, the mixture was concentrated in vacuo and purified by flash column chromatography (pentane:diethyl ether) for purification or biotage with gradient of pentane:diethyl ether. NMR yield was determined by adding 1.0 equiv. of benzylbenzoate as internal standard, the ArCOCH signal was used to determine the NMR yield.

## General procedure F .

In a $12^{*} 75 \mathrm{~mm}$ borosilicate glass tube were added the photocatalyst ( $1.0 \mathrm{~mol} \%$ ), the cyclopropane ( 0.10 $\mathrm{mmol}, 1.0$ equiv. if in the solid state), $(\mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}(7.5 \mathrm{mg}, 0.030 \mathrm{mmol}, 0.3$ equiv, ) and trapping partners ( 2.5 equiv.). The tube was closed with a rubber septum and sealed off with parafilm. Three cycles of evacuate-refill with nitrogen were performed to remove $\mathrm{O}_{2}$ and extra-dry solvent in a sealedcap bottle of Acros was added ( 0.10 M ) under nitrogen atmosphere. The cyclopropane ( $0.10 \mathrm{mmol}, 1.0$ equiv., if as a liquid) was also added at this stage. The reaction mixture was stirred at room temperature for the indicated time under irradiation with a Kessil lamp 440 nm . A flow of compressed air was used for cooling purposes or a fan on top of a stirring plate. Upon completion, the mixture was concentrated in vacuo and purified by flash column chromatography (pentane:diethyl ether) for purification or biotage with gradient of pentane:diethyl ether. The NMR yield was determined by adding 1.0 equiv. of $\mathrm{CH}_{2} \mathrm{Br}_{2}$ as internal standard, the $\operatorname{ArCOCH}$ signal was used to determine the NMR yield.

## (4,4-Dimethyl-2-phenylcyclopent-2-en-1-yl)(phenyl)methanone (2a)



Following general procedure E, starting from $\mathbf{1 a}$ ( $34.9 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.), phenyl acetylene 3 a ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) and 2 mL of MeOH , the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 100:0 to 98:2) affording (4,4-dimethyl-2-phenylcyclopent- 2-en-1yl )(phenyl)methanone 2a ( $40.8 \mathrm{mg}, 0.148 \mathrm{mmol}, 74 \%$ ) as a white solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.30$ (silica 97:3 pentane:Et $\mathrm{I}_{2}$ ). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.09-7.99(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.63-$ 7.55 (m, 1H, ArH), 7.51-7.47 (m, 2H, ArH), 7.30-7.26 (m, 2H, ArH), 7.24-7.20 (m, 2H, ArH), 7.19$7.13(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 6.23\left(\mathrm{~d}, J=1.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{3}\right)_{2}\right), 5.02(\mathrm{ddd}, J=10.2,5.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.39\left(\mathrm{dd}, J=13.0,10.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.95\left(\mathrm{dd}, J=13.0,5.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.21$ (s, 3H, CCH3), $1.18\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 201.6, 140.3, 138.5, 136.7, 135.7, 133.2, 128.8, 128.5, 127.2, 126.0, 53.5, 45.8, 44.8, 29.5, 29.0. 1 carbon is unresolved HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{20} \mathrm{NaO}^{+}$299.1406; Found 299.1411.
NMR data matching literature. ${ }^{1}$

## Dimethyl 4-benzoyl-3-phenylcyclopent-2-ene-1,1-dicarboxylate (2b)



Following general procedure E , starting from $\mathbf{1 b}$ ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $3 \mathbf{a}$ ( $30.6 \mathrm{mg}, 0.300 \mathrm{mmol}, 1.5$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 18 h. The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane : diethyl ether from 90:10 to $75: 25$ ) affording product $\mathbf{2 b}(56.8 \mathrm{mg}, 0.156 \mathrm{mmol}, 78 \%$ ) as pale yellow solid. TLC: $\mathrm{R}_{\mathrm{f}}=0.33\left(\mathrm{SiO}_{2}, 20 \% \mathrm{EtOAc}\right.$ in pentane). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.07-7.99(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7.66-7.55 (m, 1H, ArH), 7.54-7.42 (m, 2H, ArH), 7.36-7.32 (m, 2H, ArH), 7.26-7.20 (m, 3H, ArH), 6.47 (d, $\left.J=1.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CO}_{2} \mathrm{Me}\right)_{2}\right), 5.11$ (ddd, $\left.J=9.7,5.2,1.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}\right), 3.78\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CO}_{2} \mathrm{CH}_{3}\right)$, 3.76 (s, $3 \mathrm{H} \mathrm{CO}_{2} \mathrm{CH}_{3}$ ), 3.14 (dd, $J=13.7,9.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 2.73 (dd, $J=13.7,5.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.4,171.2,170.5,146.1,136.2,134.2,133.6,129.0,128.8,128.7$, 128.5, 126.6, 126.5, 66.1, 53.3, 53.2, 52.6, 37.2. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2953 (w), 1734 (s), 1684 (m), 1597 (w), 1446 (m), 1244 (s), 1211 (s), 1063 (m), 913 (m), 851 (w). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{22} \mathrm{H}_{20} \mathrm{NaO}_{5}{ }^{+}$387.1203; Found 387.1208.

## Dimethyl 4-(4-(methoxycarbonyl)benzoyl)-3-phenylcyclopent-2-ene-1,1-dicarboxylate (2c)



Following general procedure E, starting from 1c ( $64.0 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $3 \mathbf{a}$ ( $30.6 \mathrm{mg}, 0.300 \mathrm{mmol}$, 1.5 equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 48 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane : diethyl ether from 90:10 to $75: 25$ ) affording product 2c ( $56.7 \mathrm{mg}, 0.134 \mathrm{mmol}, 67 \%$ ) as yellow amorphous solid. TLC: $\mathrm{R}_{\mathrm{f}}=0.17\left(\mathrm{SiO}_{2}\right.$, Pentane: $\left.\mathrm{Et}_{2} \mathrm{O} 4: 1\right)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.19-8.13(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 8.06(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.37-7.30(\mathrm{~m}$, $2 \mathrm{H}, \mathrm{ArH}$ ), $7.26-7.20(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH}$ ), 6.47 (d, $J=1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCCH}$ ), 5.09 (ddd, $J=9.8,5.1,1.6 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{ArCOCH}$ ), 3.96 (s, 3H, $\mathrm{OCH}_{3}$ ), 3.78 (s, 3H, OCH 3 ), 3.76 (s, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), 3.13 (dd, J=13.8, 9.4 Hz , $1 \mathrm{H}, \mathrm{COCHCH}_{2}$ ), 2.74 (dd, $\left.J=13.7,5.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{COCHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) 199.1, 171.1, 170.3, 166.3, 145.8, 139.5, 134.3, 134.1, 130.2, 130.0 128.7, 128.6, 126.8, 126.5, 66.1, 53.3, 53.2, 53.1, 52.7, 37.0. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2953 (w), 2344 (w), 1729 ( s$), 1692$ (m), 1437 (m), 1283 (s), 1208 (m), 1111 (m). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{22} \mathrm{NaO}_{7}{ }^{+}$445.1258; Found 445.1251.

## (4,4-Difluoro-2-phenylcyclopent-2-en-1-yl)(phenyl)methanone (2d)



Following general procedure E, starting from 1d ( $36.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenylacetylene $\mathbf{3 a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(1 \mathrm{~mL})$, the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane: $\mathrm{Et}_{2} \mathrm{O}$ from 100:0 to $96: 4$ ) affording product $\mathbf{2 d}(30.2 \mathrm{mg}, 0.106 \mathrm{mmol}, 53 \%)$ as a white solid.

TLC: $\mathrm{R}_{\mathrm{f}}=0.39$ (silica, $96: 4$ pentane:Et ${ }_{2} \mathrm{O}$ ) MP: $102-103^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.14-8.09$ (m, 2H, ArH), $7.69-7.63(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.59-7.52(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.28-7.18(\mathrm{~m}, 5 \mathrm{H}, \mathrm{ArH}), 6.43(\mathrm{~m}$, $1 \mathrm{H}, \mathrm{ArC}=\mathrm{CH}$ ), 5.32 (dt, $J=21.0,1.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.29-3.01\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CF}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( 101 $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 193.8(\mathrm{dd}, J=6.5,4.2 \mathrm{~Hz}), 139.9(\mathrm{dd}, J=3.3,2.2 \mathrm{~Hz}), 137.3,134.0,134.0,129.9(\mathrm{t}, J$ $=256.7 \mathrm{~Hz}), 129.1,129.0,128.8,128.3,125.6,124.4(\mathrm{dd}, J=6.9,2.1 \mathrm{~Hz}), 60.0(\mathrm{t}, J=25.5 \mathrm{~Hz}), 43.1$ (t, $J=26.5 \mathrm{~Hz}) .{ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-84.5(\mathrm{dq}, J=235.5,20.5 \mathrm{~Hz}$ ), -98.5 (ddd, $J=235.3$, 13.8, 3.5 Hz ). IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2928 (w), 2856 (w), 1726 (m), 1690 (s), 1599 (m), 1448 (m), 1334 (s), 1289 (s), 1191 (s), 1134 (s), 1056 (s). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{14} \mathrm{~F}_{2} \mathrm{NaO}^{+} 307.0905$; Found 307.0891.

## (4,4-Dimethyl-2-phenylcyclopent-2-en-1-yl)(o-tolyl)methanone (2e)



Following general procedure E , starting from $\mathbf{1 e}(37.6 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $3 \mathbf{a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 18 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane : diethyl ether from 100:0 to $90: 10$ ) affording product $\mathbf{2 e}(26.4 \mathrm{mg}, 0.0910 \mathrm{mmol}, 45 \%)$ as white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.75$ (dd, $J=7.8,1.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.39 (td, $J=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), $7.33-7.12(\mathrm{~m}, 7 \mathrm{H}, \mathrm{ArH}), 6.20\left(\mathrm{~d}, \mathrm{~J}=1.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{3}\right)_{2}\right), 4.93$ (ddd, $J=9.9,5.4,1.6 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.37\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{ArCH}_{3}\right), 2.31$ (dd, $J=13.0,9.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.98 (dd, $J=13.0,5.4 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CHCH}_{2}$ ), $1.20\left(\mathrm{~d}, \mathrm{~J}=5.9 \mathrm{~Hz}, 6 \mathrm{H}, \mathrm{CCH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 205.8,140.3,138.93,138.91$, 138.2, 135.8, 132.2, 131.4, 128.5, 128.4, 127.2, 126.0, 125.7, 56.3, 45.7, 44.5, 29.5, 29.0, 21.2. HRMS (Sicrit plasma/LTQ-Orbitrap) m/z: [M] ${ }^{+}$Calcd for $\mathrm{C}_{21} \mathrm{H}_{22} \mathrm{O}^{+} 290.1665$; Found 290.1664. NMR data matching literature. ${ }^{1}$
(4,4-Dimethyl-2-phenylcyclopent-2-en-1-yl)(4-methoxyphenyl)methanone (2f)


Following general procedure E , starting from $1 \mathrm{f}(40.8 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $3 \mathbf{a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 18 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane : diethyl ether from 100:0 to $90: 10$ ) affording product $2 f(27.5 \mathrm{mg}, 0.0899 \mathrm{mmol}, 45 \%)$ as white solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.26\left(\mathrm{SiO}_{2}, 92: 8\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) . \mathrm{Mp}: 100-103{ }^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.07-$ 8.00 (m, 2H, ArH), 7.30-7.26 (m, 2H, ArH), 7.25-7.19 (m, 2H, ArH), 7.18-7.12 (m, 1H, ArH), 6.99$6.94(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 6.22\left(\mathrm{~d}, J=1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{3}\right)_{2}\right), 4.98$ (ddd, $J=10.1,5.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 3.89 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}_{3}$ ), 2.37 (dd, $J=12.9,10.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.93 (dd, $J=12.9,5.5 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $1.21\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 1.19\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 200.2, 163.6, 140.1, 138.7, 135.8, 131.1, 129.7, 128.5, 127.2, 126.0, 113.9, 55.6, 53.3, 45.8, 45.0, 29.5, 29.0. IR ( $v_{\text {max }} \mathrm{cm}^{-1}$ ) 3033 (w), 2957 (m), 2931 (m), 2864 (m), 1678 (s), 1601 (s), 1576 (m), 1509 (m), 1462 (m), 1422 ( w ), 1327 (m), 1262 (s), 1213 (s), 1170 ( s$), 1022$ (m), 916 (m), 844 (m), 771 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{21} \mathrm{H}_{22} \mathrm{NaO}_{2}{ }^{+}$329.1512; Found 329.1514.

## (4,4-Dimethyl-2-phenylcyclopent-2-en-1-yl)(4-fluorophenyl)methanone (2g)



Following general procedure E, starting from $\mathbf{1 g}(38.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $\mathbf{3 a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 18 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane : diethyl ether from 100:0 to $90: 10$ ) affording product $\mathbf{2 g}(41.2 \mathrm{mg}, 0.140 \mathrm{mmol}, 41.2 \mathrm{mg}, 70 \%)$ as pale yellow solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.36\left(\mathrm{SiO}_{2}, 97: 3\right.$ pentane:Et $\left.{ }_{2} \mathrm{O}\right) . \mathrm{Mp}: 128-131^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.10-8.03$ (m, 2H, ArH), 7.28-7.20 (m, 4H, ArH), 7.19-7.12 (m, 3H, ArH), 6.23 (d, J = $\left.1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{3}\right)_{2}\right)$, 4.97 (ddd, $J=10.2,5.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.38 (dd, $J=13.0,10.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.93 (dd, $J$ $=12.9,5.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $1.21\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 1.19\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right) .{ }^{13} \mathrm{C} \mathbf{N M R}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 200.1, 165.9 (d, $J=254.8 \mathrm{~Hz}$ ), 140.3, 138.4, 135.7, $133.0(\mathrm{~d}, J=2.9 \mathrm{~Hz}), 131.4(\mathrm{~d}, J=9.2 \mathrm{~Hz}), 128.5$, 127.3, 125.9, 115.9 (d, $J=21.9 \mathrm{~Hz}$ ), 53.6, 45.9, 44.8, 29.4, 29.0. ${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-105.3$. IR ( $v_{\text {max }}, \mathrm{cm}^{-1}$ ) 3060 (w), 3029 (w), 2953 (m), 2928 (m), 2865 (w), 1683 (s), 1599 (s), 1503 (m), 1463 (w), 1448 (m), 1410 (w), 1344 (m), 1328 (m), 1230 (s), 1209 (s), 1159 (s), 1121 (w), 1011 (m), 962 (w), 916 (m), 849 ( s$), 771$ (m), 748 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{19} \mathrm{FNaO}^{+}$317.1312; Found 317.1310.

## (4,4-Dimethyl-2-phenylcyclopent-2-en-1-yl)(4-(trifluoromethyl)phenyl)methanone (2h)



Following general procedure E, starting from $\mathbf{1 h}(48.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $\mathbf{3 a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 18 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane : diethyl ether from 100:0 to $90: 10$ ) affording product $\mathbf{2 h}(45.3 \mathrm{mg}, 0.132 \mathrm{mmol}, 66 \%)$ as pale yellow oil. TLC: $\mathrm{R}_{\mathrm{f}}=0.14\left(\mathrm{SiO}_{2}\right.$, pentane). ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.13(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.75(\mathrm{~d}, \mathrm{~J}$ $=8.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $7.26-7.15(\mathrm{~m}, 5 \mathrm{H}, \mathrm{ArH}$ ), 6.24 (d, $J=1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCCH}$ ), 5.00 (ddd, $J=10.2,5.5$, $1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 2.40 (dd, $J=13.0,10.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 1.94 (dd, J=13.0, $5.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 1.22 (s, 3H, CH3), 1.19 (s, 3H, CH3). ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 200.7,140.6,139.3,138.2,135.5,134.50$ ( $\mathrm{q}, \mathrm{J}=32.8 \mathrm{~Hz}$ ), 129.1, 128.6, 127.4, 125.9, 125.9, 54.1, 46.0, 44.6, 29.4, 29.0. Carbon $\mathrm{CF}_{3}$ is unresolved due to overlapping with other signals. ${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$-63.1. IR ( $\mathrm{Vmax}, \mathrm{cm}^{-}$ ${ }^{1}$ ) 2958 (w), 1690 (m), 1321 (s), 1171 (m), 1131 (s), 1068 (m), 1013 (w), 855 (m). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{21} \mathrm{H}_{19} \mathrm{~F}_{3} \mathrm{NaO}^{+}$367.1280; Found 367.1285.

## Tert-butyl 4-benzoyl-3-phenylcyclopent-2-ene-1-carboxylate (2i)



Following general procedure E , starting from $\mathbf{1 i}(49.3 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $3 \mathbf{a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 48 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane : diethyl ether from $100: 0$ to $80: 20$ ) affording product $\mathbf{2 i}$ ( $34.6 \mathrm{mg}, 0.994 \mathrm{mmol}, 50 \%$ ) as off-white amorphous solid, the product was isolated as a mixture of 2 diastereomers. The ratio was determined in the crude mixture using the signal at PhCOCH 4.84 ppm (major), 5.32 ppm (minor) of PhCOCH (dr: $68: 32$ ). The NMR is reported for the major diastereoisomer only. The relative configuration of the major diastereoisomer was not determined.
TLC: $\mathrm{R}_{\mathrm{f}}=0.39\left(\mathrm{SiO}_{2}, 90: 10\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.00-7.95(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7.54-7.48 (m, 1H, ArH), 7.45-7.41 (m, 2H, ArH), 7.27-7.22 (m, 2H, ArH), 7.21-7.14 (m, 3H, ArH), 6.34 (dd, $J=2.9,1.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCO}_{2} \mathrm{tBu}$ ), 4.84 (ddt, $J=9.8,5.9,1.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 3.67 (dddd, $J=8.8$, $5.1,2.9,1.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CHCO}_{2} \mathrm{tBu}$ ), 2.68 (ddd, $J=13.4,10.0,9.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CHCH}_{2}$ ), 2.42 (dt, $J=$ $\left.13.4,5.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CHCH}_{2}\right), 1.38\left(\mathrm{~s}, 9 \mathrm{H}, \mathrm{CO}_{2} \mathrm{C}\left(\mathrm{CH}_{3}\right)_{3} .{ }^{13} \mathrm{C}\right.$ NMR (101 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 199.9,172.0$, 143.7, 136.4, 135.2, 133.2, 128.9, 128.8, 128.6, 127.8, 127.8, 126.2, 81.1, 53.5, 51.6, 32.4, 28.2. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2971 (w), 2966 (w), 2932 (w), 1723 ( s$), 1681$ (m), 1598 (w), 1451 (m), 1367 (m), 1211 ( s$)$, 1150 (s), 847 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{23} \mathrm{H}_{24} \mathrm{NaO}_{3}{ }^{+}$371.1618; Found 371.1612.

## (2,4-Diphenylcyclopent-2-en-1-yl)(phenyl)methanone (2j)



Following general procedure E, starting from 1 j ( $44.5 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $3 \mathbf{a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 48 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane :
diethyl ether from 100:0 to $90: 10$ ) affording product $\mathbf{2 j}$ ( $9.7 \mathrm{mg}, 0.030 \mathrm{mmol}, 15 \%$ ) as a white solid. The ratio was determined in the crude mixture using the signal of $\mathrm{ArC}=\mathrm{CHAr} 6.39 \mathrm{ppm}$ (major), 6.54 ppm (minor) (dr: 87:13). The NMR data is reported for the major diastereoisomer only. Comparison with reported data allowed to assign the cis configuration to the major diastereoisomer. ${ }^{8}$
TLC: $\mathrm{R}_{\mathrm{f}}=0.30\left(\mathrm{SiO}_{2}, 97: 3\right.$ pentane:Et $\left.\mathrm{t}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.13-7.98(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7.62-7.52 (m, 1H, ArH), 7.51-7.45 (m, 2H, ArH), 7.36-7.30 (m, 6H, ArH), 7.29-7.27 (m, 1H, ArH), $7.25(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.24-7.19(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 6.39(\mathrm{dd}, J=2.5,1.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArC=CHAr}), 5.10$ (ddt, $J=$ $9.6,7.2,2.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 4.20 (ddt, $\left.J=9.0,6.6,2.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CHAr}\right), 3.20-3.02$ (m, 1H, $\mathrm{CHCH}_{2}$ ), 2.02 (ddd, $J=13.6,7.3,6.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.3,145.0$, 143.0, 136.7, 135.6, 133.3, 133.2, 128.9, 128.8, 128.7, 128.6, 127.9, 127.5, 126.7, 126.2, 53.7, 51.5, 39.8. HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{20} \mathrm{NaO}^{+} 347.1406$; Found 347.1402.

NMR data matching literature. ${ }^{8}$

## Phenyl(2-phenyl-4-(trifluoromethyl)cyclopent-2-en-1-yl)methanone (2k)



Following general procedure E, starting from $\mathbf{1 k}(42.8 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $3 \mathbf{a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 72 h. The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane : diethyl ether from 100:0 to $90: 10$ ) affording product $\mathbf{2 k}(25.8 \mathrm{mg}, 81.6 \mu \mathrm{~mol}, 41 \%)$ as a pale yellow oil. The ratio was determined in the crude mixture using the signal of ArCOCH 5.03 ppm (major), 5.15 ppm (minor) (dr: 62:38). The NMR data is reported for the major diastereoisomer only.
TLC: $\mathrm{R}_{\mathrm{f}}=0.52\left(\mathrm{SiO}_{2}, 8: 1\right.$ pentane $\left.: \mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.05-7.99(\mathrm{~m}, 2 \mathrm{H}), 7.64-7.57$ (m, 1H), $7.53-7.48(\mathrm{~m}, 2 \mathrm{H}), 7.37-7.31(\mathrm{~m}, 2 \mathrm{H}), 7.30-7.26(\mathrm{~m}, 2 \mathrm{H}), 7.25-7.23(\mathrm{~m}, 1 \mathrm{H}), 6.23(\mathrm{dd}, \mathrm{J}$ $=2.6,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.12-4.96(\mathrm{~m}, 1 \mathrm{H}), 3.74-3.57(\mathrm{~m}, 1 \mathrm{H}), 2.85(\mathrm{ddd}, J=13.9,10.3,9.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.23$ (dt, $J=13.9,6.4 \mathrm{~Hz}, 1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.2,147.6,136.1,134.5,133.6,129.0,128.8$, 128.7, 128.4, 126.4, $122.75(\mathrm{q}, J=2.8 \mathrm{~Hz}) 53.2 .49 .67(\mathrm{q}, J=29.3 \mathrm{~Hz}) 29.42(\mathrm{t}, J=2.5 \mathrm{~Hz}) . \mathrm{CF}_{3}$ carbon is around 128 , J coupling is unresolved due to overlapping. ${ }^{19} \mathbf{F} \mathbf{N M R}\left(376 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta-71.4$. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 3060 (w), 2923 (w), 1685 (m), 1597 (w), 1448 (m), 1268 (s), 1151 (s), 1114 (s), 757 (m). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{19} \mathrm{H}_{15} \mathrm{~F}_{3} \mathrm{NaO}^{+} 339.0967$; Found 339.0970.

## Phenyl(3-phenylspiro[4.5]dec-3-en-2-yl)methanone (2I)



Following general procedure E, starting from $11(42.2 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $\mathbf{3 a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 18 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane : diethyl ether from 100:0 to $95: 5$ ) affording product $\mathbf{2 l}(34.8 \mathrm{mg}, 0.110 \mathrm{mmol}, 55 \%$ ) as a white solid.

TLC: $\mathrm{R}_{\mathrm{f}}=0.35$ (silica $97: 3$ pentane:Et $\mathrm{I}_{2}$ ). Mp: $146-148^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.08-8.03$ ( $\mathrm{m}, 2 \mathrm{H}, \mathrm{ArH}$ ), 7.62-7.57 (m, 1H, ArH), 7.53-7.47 (m, 2H, ArH), 7.31-7.27 (m, 2H, ArH), 7.25-7.20 (m, 2H, ArH), 7.18-7.13 (m, 1H, ArH), 6.39 (d, J = $\left.1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{2}\right)_{5}\right), 4.99$ (ddd, $J=10.4,5.4$, $1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.38 (dd, $J=13.2,10.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.93 (dd, $J=13.2,5.3 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CHCH}_{2}$ ), 1.66-1.34 (m, 10H, cyclohexyl CH). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 201.8, 138.7, 136.6, $135.8,133.2,128.8,128.5,127.2,126.0,52.8,50.1,41.7,38.4,37.8,26.0,23.1,23.5 .2$ carbons of aromatic ring are unresolved or overlapping. HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{23} \mathrm{H}_{24} \mathrm{NaO}^{+} 339.1719$; Found 339.1717. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 3061 (w), 3026 (w), 2925 (s), 2852 (m), 1684 (s), 1595 (w), 1494 (w), 1451 (m), 1346 (w), 1328 (m), 1209 (s), 1015 (w), 968 (w), 932 (w), 914 (w), 849 (w), 766 (m), 736 (m).

## Phenyl(7-phenylspiro[3.4]oct-7-en-6-yl)methanone (2m)



Following general procedure E, starting from $1 \mathrm{~m}(37.2 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $3 \mathbf{a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 48 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane : diethyl ether from $100: 0$ to $95: 5$ ) affording product $\mathbf{2 m}(11.5 \mathrm{mg}, 0.0399 \mathrm{mmol}, 20 \%)$ as a white solid. TLC: $\mathrm{R}_{\mathrm{f}}=0.32$ (silica $97: 3$ pentane:Et ${ }_{2} \mathrm{O}$ ). Mp: 99-102 ${ }^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.07-8.01$ (m, 2H, ArH), 7.62-7.56 (m, 1H, ArH), 7.53-7.46 (m, 2H, ArH), 7.33-7.25 (m, 2H, ArH), 7.25-7.19 (m, 2H, ArH), 7.19-7.13 (m, 1H, ArH), 6.57 (d, J = $\left.1.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{2}\right)_{3}\right), 4.93$ (ddd, J = 9.9, 4.6, 1.4 $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.63 (dd, $J=13.2,9.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 2.29-2.20 (m, 3H, CHCH2 + cyclobutyl $\mathrm{CH}_{2}$ ), 2.13-1.95 (m, 2H, cyclobutyl $\mathrm{CH}_{2}$ ), 1.94-1.81 (m, 2H, cyclobutyl $\mathrm{CH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( 101 MHz , $\mathrm{CDCl}_{3}$ ) $\delta 201.3,139.5,138.1,136.6,135.6,133.2,128.9,128.8,128.5,127.3,126.0,53.3,52.7$, 44.7, 35.2, 35.0, 16.7. IR ( $v_{\text {max }}, \mathrm{cm}^{-1}$ ) 3061 (w), 3036 (w), 2951 (m), 2928 (m), 2863 (w), $1683(\mathrm{~s})$, 1599 (m), 1581 (w), 1497 (w), 1447 (m), 1343 (m), 1331 (m), 1213 (s), 1179 (m), 1011 (m), 910 (m), 763 (m), $734(\mathrm{~m})$. HRMS (ESI/QTOF) m/z: $[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{21} \mathrm{H}_{20} \mathrm{NaO}^{+} 311.1406$; Found 311.1406.

## (4,4-Dimethyl-2-phenylcyclopent-2-en-1-yl)(naphthalen-2-yl)methanone (2n)



Following general procedure E, starting from $\mathbf{1 n}(44.8 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and phenyl acetylene $\mathbf{3 a}$ ( $102 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 18 h. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane : diethyl ether from 100:0 to $90: 10$ ) affording product $\mathbf{2 n}(44.3 \mathrm{mg}, 0.135 \mathrm{mmol}, 68 \%)$ as pale yellow sticky oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.30\left(\mathrm{SiO}_{2}, 97: 3\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.61-8.58(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 8.09$ (dd, $J=8.6,1.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 8.02-7.98 (m, 1H, ArH), 7.95-7.88 (m, 2H, ArH), 7.64-7.56 (m, 2H, ArH), 7.33-7.29 (m, 2H, ArH), 7.24-7.19 (m, 2H, ArH), 7.18-7.13 (m, 1H, ArH), 6.27 (d, J = 1.5 Hz , $\left.1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{3}\right)_{2}\right), 5.19$ (ddd, $J=10.2,5.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.48 (dd, $J=13.0,10.2 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CHCH}_{2}$ ), $2.02\left(\mathrm{dd}, J=13.0,5.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.25\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 1.22\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR
(101 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 201.7,140.3,138.6,135.7,134.0,132.7,130.3,129.8,128.7,128.6,128.5,127.9$, 127.2, 126.9, 126.0, 124.7, 53.6, 45.9, 45.0, 29.5, 29.0. IR ( $v_{\max } \mathrm{cm}^{-1}$ ) 3055 (w), 3033 (w), 2953 (m), 2864 (w), 1678 (s), 1627 (m), 1497 (w), 1465 (m), 1364 (m), 1321 (m), 1277 (m), 1182 (m), 1123 (m), 1024 (w), 957 (w), 912 (m), 863 (m), 824 (m), 763 (s), 740 (m). HRMS (ESI/QTOF) m/z: $[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{22} \mathrm{NaO}^{+} 349.1563$; Found 349.1564.

## (2-([1,1'-biphenyl]-4-yl)-4,4-dimethylcyclopent-2-en-1-yl)(phenyl)methanone (2o)



Following general procedure E, starting from $\mathbf{1 a}$ ( $34.9 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 b}$ ( 178 mg , $1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 42 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 100:0 to $90: 10$ ) affording $20(28.2 \mathrm{mg}, 0.0801 \mathrm{mmol}, 40 \%$ ) as a pale yellow solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.30\left(\mathrm{SiO}_{2}, 96: 4\right.$ pentane $\left.: \mathrm{Et}_{2} \mathrm{O}\right) . \mathrm{Mp}: 92-93.5^{\circ} \mathrm{C}$
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.11-8.04(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.63-7.58(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.56-7.45(\mathrm{~m}, 6 \mathrm{H}, \mathrm{ArH})$, $7.43-7.28(\mathrm{~m}, 5 \mathrm{H}, \mathrm{ArH}), 6.29\left(\mathrm{~d}, J=1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{3}\right)_{2}\right), 5.06$ (ddd, $J=10.2,5.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{C}(\mathrm{O}) \mathrm{CH}), 2.43\left(\mathrm{dd}, J=12.9,10.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.98\left(\mathrm{dd}, J=13.0,5.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.24(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{CCH}_{3}$ ), $1.20\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 201.6, 141.0, 140.4, 139.9, 138.1, 136.6, 134.8, 133.3, 128.8, 127.3, 127.2, 127.1, 126.4, 53.5, 45.9, 44.9, 29.5, 29.0. IR ( $v_{\max }, \mathrm{cm}^{-1}$ ) 3061 (w), 3033 (w), 2953 (m), 2935 (m), 2863 (w), 1685 (s), 1599 (m), 1581 (w), 1487 (m), 1444 (m), 1335 (m), 1206 (s), 1179 (m), 1011 (m), 914 (m), 835 (s), 765 (m), $730(\mathrm{~m})$. HRMS (ESI/QTOF) $\mathrm{m} / \mathrm{z}$ : $[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{26} \mathrm{H}_{24} \mathrm{NaO}^{+} 375.1719$; Found 375.1717.

## (2-(4-Methoxyphenyl)-4,4-dimethylcyclopent-2-en-1-yl)(phenyl)methanone (2p)



Following general procedure E, starting from $\mathbf{1 a}$ ( $34.9 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $3 \mathbf{c}$ ( 132 mg , $1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 100:0 to $90: 10$ ) affording $2 \mathbf{p}(33.7 \mathrm{mg}, 0.110 \mathrm{mmol}, 55 \%)$ as a pale yellow oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.34\left(\mathrm{SiO}_{2}, 92: 8\right.$ pentane:Et $\left.\mathrm{t}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.07-8.00(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.62-$ 7.56 (m, 1H, ArH), 7.52-7.47 (m, 2H, ArH), 7.23-7.19 (m, 2H, ArH), 6.78-6.74 (m, 2H, ArH), $6.10(\mathrm{~d}$, $\left.J=1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{3}\right)_{2}\right), 4.98$ (ddd, $\left.J=10.2,5.4,1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}\right), 3.75\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.38$ (dd, $J=12.9,10.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.94 (dd, $J=13.0,5.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $1.20\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 1.17$ (s, 3H, $\mathrm{CCH}_{3}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.8,158.8,138.3,137.9,136.7,133.2,128.9,128.8$,
128.5, 127.2, 113.9, 55.4, 53.8, 45.8, 44.9, 29.6, 29.1. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) $3040(\mathrm{w}), 2957(\mathrm{~m}), 2932(\mathrm{~m})$, 2863 (w), 2835 (w), 1682 (s), 1608 (m), 1577 (w), 1513 (s), 1461 (m), 1444 (m), 1335 (m), 1296 (m), 1249 (s), 1209 (m), 1179 (s), 1119 (w), 1033 (m), 917 (w), 835 (m), 708 (m). HRMS (ESI/QTOF) m/z: $[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{21} \mathrm{H}_{22} \mathrm{NaO}_{2}{ }^{+}$329.1512; Found 329.1508.

## (2-(4-Bromophenyl)-4,4-dimethylcyclopent-2-en-1-yl)(phenyl)methanone (2q)



Following general procedure E, starting from $\mathbf{1 a}$ ( $34.9 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 d}$ ( 181 mg , $1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 100:0 to $95: 5$ ) affording $\mathbf{2 q}(42.6 \mathrm{mg}, 0.120 \mathrm{mmol}, 60 \%)$ as a yellow sticky oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.41\left(\mathrm{SiO}_{2}, 98: 2\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.06-7.99(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.64-$ $7.55(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.50(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.44-7.26(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.19-7.09(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 6.22(\mathrm{~d}, \mathrm{~J}=1.5$ $\left.\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CH}_{3}\right)_{2}\right), 4.98$ (ddd, $J=10.2,5.4,1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 2.40 (dd, $J=13.0,10.2 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CHCH}_{2}$ ), 1.95 (dd, $\mathrm{J}=13.0,5.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $1.21\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right), 1.17\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CCH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR (201 $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.3,141.1,137.5,136.4,134.8,133.4,131.6,128.9,128.8,127.6,121.0,53.5,46.0$, 44.8, 29.4, 28.9. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2983 (s), 2885 (s), 2832 (s), 1740 (w), 1501 (m), 1297 (w), 1221 (w), 1152 (w), 1054 (w). HRMS (Sicrit plasma/LTQ-Orbitrap) m/z: [M] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{19} \mathrm{BrO}^{+}$354.0614; Found 354.0603.

Dimethyl 3-([1,1'-biphenyl]-4-yl)-4-benzoylcyclopent-2-ene-1,1-dicarboxylate (2r)


Following general procedure E, starting from $\mathbf{1 b}(52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 b}$ ( 53.4 mg , 0.300 mmol , 1.5 equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, in 16 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 100:0 to 90:10) affording $\mathbf{2 r}$ ( $57.7 \mathrm{mg}, 0.131 \mathrm{mmol}, 65 \%$ ) as a pale yellow sticky oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.31\left(\mathrm{SiO}_{2} 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $\left.400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.11-8.02(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7.75-7.58 (m, 1H, ArH), 7.58-7.46 (m, 6H, ArH), $7.41(\mathrm{~m}, 4 \mathrm{H}, \mathrm{ArH}), 7.38-7.27(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 6.52(\mathrm{~d}, \mathrm{~J}$ $\left.=1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CO}_{2} \mathrm{Me}\right)_{2}\right), 5.15$ (ddd, $\left.J=9.6,5.2,1.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}\right), 3.78\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CO}_{2} \mathrm{CH}_{3}\right), 3.77$ (s, 3H, $\mathrm{CO}_{2} \mathrm{CH}_{3}$ ), 3.17 (dd, $J=13.7,9.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 2.75 (dd, $J=13.6,5.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 199.3,171.1,170.3,145.5,141.1,140.5,136.1,133.5,133.1,128.9,128.8$, 128.7, 127.4, 127.2, 127.0, 126.8, 126.5, 66.0, 53.1, 53.0, 52.5, 37.1. IR ( $\left.\mathrm{v}_{\max }, \mathrm{cm}^{-1}\right) 2953(\mathrm{w}), 2255$ (w), 1733 (s), 1683 (m), 1597 (w), 1435 (m), 1240 (s), 1210 (s), 1008 (m), 909 (m). HRMS (ESI/QTOF) $\mathrm{m} / \mathrm{z}:[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{28} \mathrm{H}_{24} \mathrm{NaO}_{5}{ }^{+}$463.1516; Found 463.1525.


Following general procedure E, starting from $\mathbf{1 b}(52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $3 \mathbf{c}(39.6 \mathrm{mg}$, $0.300 \mathrm{mmol}, 1.5$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 90:10 to $75: 25$ ) affording $2 \mathrm{~s}(64.6 \mathrm{mg}, 0.164 \mathrm{mmol}, 82 \%)$ as a pale yellow solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.21\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). Mp: $106-108{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.07-7.99$ (m, 2H, ArH), 7.65-7.56 (m, 1H, ArH), 7.55-7.45 (m, 2H, ArH), 7.31-7.22 (m, 2H, ArH), 6.82-6.74 (m, $2 \mathrm{H}, \mathrm{ArH}$ ), 6.35 (d, J=1.5 Hz, 1H, CHC(CO2Me) $)_{2}$, 5.06 (ddd, J=9.7, 5.1, $\left.1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}\right), 3.77$ (s, 3H, OCH 3 ), $3.75\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), 3.12 (dd, J=13.7, $9.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 2.72 (dd, J=13.7, 5.2 Hz , $1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.6,171.4,170.6,159.8,145.5,136.2,133.5,128.9$, 128.8, 127.8, 126.9, 124.5, 114.0, 66.1, 55.4, 53.2, 53.1, 52.8, 37.2. IR ( $\mathrm{v}_{\mathrm{max}} \mathrm{cm}^{-1}$ ) 2954 (w), $2840(\mathrm{w})$, 2360 (w), 1752 (m), 1729 (s), 1723 (s), 1681 (m), 1608 (m), 1512 (m), 1445 (m), 1031 (m), 831 (s). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{23} \mathrm{H}_{22} \mathrm{NaO}_{6}{ }^{+}$417.1309; Found 417.1313.

## Dimethyl 4-benzoyl-3-(4-chlorophenyl)cyclopent-2-ene-1,1-dicarboxylate (2t)



Following general procedure E, starting from $\mathbf{1 b}$ ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 e}(41.0 \mathrm{mg}$, 0.300 mmol , 1.5 equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 95:5 to $85: 15$ ) affording 2 t ( $59.9 \mathrm{mg}, 0.151 \mathrm{mmol}, 75 \%$ ) as a sticky oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.18\left(\mathrm{SiO}_{2}, 90: 10\right.$ pentane:EtOAc).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ס 8.01-7.94 (m, 2H, ArH), 7.62-7.52 (m, 1H, ArH), 7.47 (t, J=7.7 Hz, 2H, ArH), 7.25-7.15 (m, 4H, ArH), 6.41 (d, $\left.J=1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CO}_{2} \mathrm{Me}\right)_{2}\right), 5.03$ (ddd, J=9.7, 5.2, 1.6 Hz , $1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.74\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.71\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.10\left(\mathrm{dd}, \mathrm{J}=13.7,9.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.69$ (dd, $\left.J=13.7,5.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C} \operatorname{NMR}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 199.1,171.1,170.2,145.0,136.0$, 134.2, 133.7, 132.8, 129.0, 128.8, 127.7, 127.2, 66.1, 53.3, 53.2, 52.6, 37.2. One carbon is unresolved or overlapped. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2953 (w), 2258 (w), 1733 (s), 1683 (m), 1492 (m), 1435 (m), 1240 (s), 1083 (m), 1011 (m), 910 (m), 829 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{22} \mathrm{H}_{19} \mathrm{ClNaO}_{5}{ }^{+} 421.0813$; Found 421.0812.

## Dimethyl 4-benzoyl-3-(4-(methoxycarbonyl)phenyl)cyclopent-2-ene-1,1-dicarboxylate (2u)



Following general procedure E , starting from $\mathbf{1 b}$ ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 f}$ ( 160 mg , $1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 85:15 to $75: 25$ ) affording $\mathbf{2 u}(43.9 \mathrm{mg}, 0.104 \mathrm{mmol}, 52 \%)$ as a sticky oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.19\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.10-7.98(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7.96-7.89 (m, 2H, ArH), 7.67-7.56 (m, 1H, ArH), 7.56-7.46 (m, 2H, ArH), 7.42-7.33 (m, 2H, ArH), 6.58 (d, $\left.J=1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CO}_{2} \mathrm{Me}\right)_{2}\right)$, 5.12 (ddd, $\left.J=9.7,5.2,1.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}\right)$, $3.88\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, 3.78 (s, 3H, OCH3), 3.76 (s, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ) 3.16 (dd, $J=13.7,9.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 2.74 (dd, $J=13.7,5.2$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.1,170.9,170.1,166.8,145.3,138.7,136.0,133.8$, 130.0, 129.8, 129.1, 129.0, 128.8, 126.4, 66.2, 53.4, 53.3, 52.6, 52.3, 37.2. IR ( $\left.\mathrm{v}_{\max }, \mathrm{cm}^{-1}\right) 2954(\mathrm{w})$, 1725 (s), 1609 (w), 1437 (m), 1285 (s), 1112 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{22} \mathrm{NaO}_{7}{ }^{+} 445.1258$; Found 445.1262.

## Dimethyl 4-benzoyl-3-(thiophen-3-yl)cyclopent-2-ene-1,1-dicarboxylate (2v)



Following general procedure E, starting from $\mathbf{1 b}(52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 g}$ ( 60.1 mg , 0.300 mmol , 1.5 equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 85:15 to $75: 25$ ) affording $2 v(59.9 \mathrm{mg}, 0.162 \mathrm{mmol}, 81 \%)$ as a yellow sticky oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.31\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.06-8.00(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.66-7.57$ (m, 1H, ArH), 7.51 (dd, J=8.3, 7.0 Hz, 2H, ArH), 7.27-7.17 (m, 2H, ArH), 6.97 (dd, J = 2.7, $1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.35 (d, $\left.J=1.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHC}\left(\mathrm{CO}_{2} \mathrm{Me}\right)_{2}\right), 4.98$ (ddd, $\left.J=9.7,4.9,1.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}\right)$, 3.77 (s, 3H, OCH3), 3.75 (s, 3H, OCH3), 3.10 (dd, $J=13.7,9.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 2.74 (dd, $J=13.7,4.9$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 199.6, 171.2, 170.5, 141.1, 136.3, 136.2, 133.6, 129.0, 128.8, 126.3, 126.2, 126.0, 122.9, 66.2, 53.4, 53.2, 53.1, 37.2. HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{NaO}_{5} \mathrm{~S}^{+} 393.0767$; Found 393.0760. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) $2954(\mathrm{w}), 1734(\mathrm{~s}), 1684(\mathrm{~m}), 1435(\mathrm{~m})$, 1243 (s), 1213 (s), 1082 (m).

## 3-Ethyl 1,1-dimethyl 4-benzoylcyclopent-2-ene-1,1,3-tricarboxylate (2w)



Following general procedure E, starting from $\mathbf{1 b}$ ( $34.9 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 h}$ ( 98.0 mg , $1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 72 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to $60: 40$ ) affording product $\mathbf{2 w}$ ( $26.6 \mathrm{mg}, 73.9 \mu \mathrm{~mol}, 37 \%$ yield) as colorless oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.20\left(\mathrm{SiO}_{2}, 2: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.02-7.94(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.63$ $-7.56(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.51-7.44(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 6.96(\mathrm{~d}, J=1.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{COCHCCH}), 4.90$ (ddd, $J=9.5$, $5.7,1.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 4.16 (qd, $J=7.1,1.8 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{COOCH}_{2} \mathrm{CH}_{3}$ ), $3.79\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.76(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), $3.04\left(\mathrm{dd}, J=13.9,9.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCHCH} 2\right.$ ), $2.62\left(\mathrm{dd}, J=13.9,5.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCHCH}_{2}\right.$ ), $1.20\left(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{COOCH}_{2} \mathrm{CH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.3,170.0,169.3,163.6,140.6$, 139.9, 136.1, 133.5, 128.9, 128.8, 66.5, 61.2, 53.5, 53.4, 50.8, 36.7, 14.1. IR ( $\left.\mathrm{v}_{\max }, \mathrm{cm}^{-1}\right) 2957$ (w), 2852 (w), 1738 (s), 1686 (m), 1447 (m), 1303 (m), 1240 (s), 1063 (m), 877 (w) HRMS (ESI/QTOF) m/z: [M + $\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{NaO}_{7}{ }^{+} 383.1101$; Found 383.1093.

## Dimethyl 3-acetyl-4-benzoylcyclopent-2-ene-1,1-dicarboxylate (2x)



Following general procedure E, starting from $\mathbf{1 b}$ ( $34.9 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 i}(68.0 \mathrm{mg}$, $1.00 \mathrm{mmol}, 5.0$ equiv.) in $\mathrm{MeOH}(2 \mathrm{~mL})$, the reaction mixture was stirred for 72 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether 80:20 to $60: 40$ ) affording product $\mathbf{2 x}(29.0 \mathrm{mg}, 0.0880 \mathrm{mmol}, 44 \%$ yield) as a colorless oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.29\left(\mathrm{SiO}_{2}, 3: 1\right.$ pentane:Et $\left.{ }_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.05-7.92(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.63$ $-7.54(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}$ ), $7.53-7.44$ (m, 2H, ArH), 6.86 (d, J=1.6 Hz, 1H, MeCOCCH), 4.91 (ddd, J=9.5, $5.7,1.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}), 3.80\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.78\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), 2.99 (dd, J=13.9, $9.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}$ ), 2.59 (dd, $J=13.9,5.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $2.42\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{COCH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.3,195.5$, 169.9, 169.2, 148.2, 140.2, 136.1, 133.5, 128.9, 128.8, 67.1, 53.6, 53.5, 50.5, 36.3, 27.0. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-}$ ${ }^{1}$ ) 2957 (w), 1737 (s), 1676 (s), 1451 (m), 1436 (m), 1239 (s), 1065 (m), 863 (m). HRMS (ESI/QTOF) $\mathrm{m} / \mathrm{z}:[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{18} \mathrm{NaO}_{6}{ }^{+}$353.0996; Found 353.1003.

## (4,4-Dimethyl-2-phenylcyclopentyl)(phenyl)methanone (4a)



Following general procedure E, starting from $\mathbf{1 a}$ ( $34.9 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{5 a}$ ( 105 mg , $1.00 \mathrm{mmol}, 5.0$ equiv.) and 2 mL CH 3 CN the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 100:0 to $95: 5$ ) affording 4 a ( $45.6 \mathrm{mg}, 0.164 \mathrm{mmol}, 82 \%$ ) as a white solid. The isolated product is a mixture of 2 diastereomers. The diastereomeric ratio ( $\mathrm{dr} 75: 25$ ) was determined by integrating the NMR signals of total ArCOCH + ArCH. Major ( 4.35 and 3.81 ppm ) and Minor ( 3.96 ppm , for 2 H ) in the crude mixture. The NMR data is reported for the major diastereomer (cis) only, the data is matching the literature. ${ }^{16}$
${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.57-7.52(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.38-7.33(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.25-7.19(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH})$, 6.98-6.91 (m, 4H, ArH), 4.35 (ddd, $J=10.4,8.9,7.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 3.81 (td, $J=10.5,7.5 \mathrm{~Hz}, 1 \mathrm{H}$, ArCH), 2.32 (dd, $J=13.1,9.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 2.00 (dd, $J=12.8,10.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 1.93 (ddd, $J$ $\left.=12.7,7.6,1.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.77-1.71\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.28\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.18\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 202.4,142.2,138.3,132.2,128.6,128.10,128.07,127.8,126.1,51.1,49.1$, 48.6, 43.4, 38.6, 29.5, 28.7. HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{NaO}^{+} 301.1563$; Found 301.1568.

NMR data matching literature. ${ }^{16}$

## Dimethyl 3-benzoyl-4-phenylcyclopentane-1,1-dicarboxylate (4b)



Following general procedure E, starting from $\mathbf{1 b}$ ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and 5 a ( 31.4 mg , $0.300 \mathrm{mmol}, 1.5$ equiv.) and $2 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 85:15 to $75: 25$ ) affording $\mathbf{4 b}(65.9 \mathrm{mg}, 0.180 \mathrm{mmol}, 90 \%$ for both diastereomers) as a colorless oil. The dr (67:33) was determined by integrating the NMR signals of $\operatorname{ArCOCH} 4.04 \mathrm{ppm}$ (major), 4.32 ppm (minor).

## 4b1 - major diastereoisomer

TLC: $\mathrm{R}_{\mathrm{f}}=0.50\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.87-7.76(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7.54-7.47 (m, 1H, ArH), 7.42-7.35 (m, 2H, ArH), 7.28-7.21 (m, 4H, ArH), 7.17 (ddt, J = 7.0, 5.6, 2.3 $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 4.04 (td, $J=9.9,8.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 3.80\left(\mathrm{~m}, 7 \mathrm{H}, \mathrm{ArCH}\right.$ and $\left.\mathrm{OCH}_{3}\right), 3.03(\mathrm{dd}, J=13.7$, $8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 2.95 (dd, $J=13.7,8.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $2.50\left(\mathrm{dd}, J=13.7,9.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right.$ ), 2.42 (dd, $J=13.7,11.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 200.0,172.9,171.9,141.8$, 136.7, 133.3, 128.70, 128.65, 128.6, 127.5, 126.9, 59.3, 53.9, 53.2, 53.1, 47.8, 41.9, 39.3. IR ( $\mathrm{v}_{\mathrm{max}} \mathrm{cm}^{-}$ ${ }^{1}$ ) 2953 (w), 1731 (s), 1681 (m), 1598 (w), 1447 (m), 1253 (s), 1163 (m), 1097 (m), 1006 (w), 750 (m).
HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{22} \mathrm{H}_{22} \mathrm{NaO}_{5}{ }^{+}$389.1359; Found 389.1362.

## 4b2 minor diastereomer

TLC: $\mathrm{R}_{\mathrm{f}}=0.45\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.57-7.51(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.37$ (ddt, $J=6.8,5.9,1.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), $7.25-7.20$ (m, 2H, ArH), 7.05-6.92 (m, 5H, ArH), 4.32 (dt, J = 9.4, $7.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), 3.78-3.74 (m, 1H, ArCH), 2.95 (dd, $J=$ $13.9,7.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $2.85-2.70\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.66$ (ddd, $J=13.9,7.3,1.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.1,173.3,172.0,139.8,137.6,132.6,128.3,128.2,128.2,128.1$, 126.8, 59.6, 53.2, 53.0, 50.2, 48.2, 40.2, 36.6. IR (v $\mathrm{m}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2953 (w), 1731 (s), 1679 (m), 1598 (w), 1447 (m), 1255 (s), 1220 (s), 1164 (m), 1078 (m). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{22} \mathrm{H}_{22} \mathrm{NaO}_{5}{ }^{+}$389.1359; Found 389.1350.

## (4,4-Dimethyl-2-phenylcyclopentyl)(4-methoxyphenyl)methanone (4c)



Following general procedure E, starting from $\mathbf{1 f}(40.8 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{5}$ ( 105 mg , $1.00 \mathrm{mmol}, 5.0$ equiv.) and $2 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 100:0 to $85: 15$ ) affording $4 \mathbf{c}$ ( $51.7 \mathrm{mg}, 0.168 \mathrm{mmol}, 84 \%$ for both diastereomers) as a colorless oil. The dr (71:29) was determined by integrating the NMR signals of ArH 7.57 ppm (major), 7.81 ppm (minor) of crude mixture. NMR reported for major diastereomer.
TLC: $\mathrm{R}_{\mathrm{f}}=0.47\left(\mathrm{SiO}_{2}, 90: 10\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.60-7.53(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.26$ - 7.19 (m, 2H, ArH), 7.03 - 6.96 (m, 3H, ArH), $6.75-6.68$ (m, 2H, ArH), 4.30 (ddd, J = 10.4, 8.8, 7.5 $\mathrm{Hz}, 1 \mathrm{H}, \operatorname{ArCOCH}$ ), $3.96-3.84(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArCH}), 3.79\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.31(\mathrm{dd}, J=13.1,8.8 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CHCH}_{2}$ ), $2.03-1.97\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.92$ (ddd, $J=12.7,7.4,1.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $1.75-1.68(\mathrm{~m}$, $1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $1.28\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{3}\right), 1.17\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 200.7,162.8$, 142.3, 131.4, 130.8, 130.4, 128.6, 127.8, 113.2, 55.5, 50.6, 49.0, 48.7, 43.5, 38.6, 29.6, 28.8. IR (v $\mathrm{v}_{\max }$, $\mathrm{cm}^{-1}$ ) 2952 (m), 2867 (w), 1671 (m), 1602 (s), 1510 (m), 1462 (m), 1366 (m), 1255 (s), 1172 (s), 1032 (m). HRMS (Sicrit plasma/LTQ-Orbitrap) m/z: [M + H] ${ }^{+}$Calcd for $\mathrm{C}_{21} \mathrm{H}_{25} \mathrm{O}_{2}{ }^{+}$309.1849; Found 309.1849.

## (4,4-Dimethyl-2-phenylcyclopentyl)(4-(trifluoromethyl)phenyl)methanone (4d)



Following general procedure E, starting from $\mathbf{1 h}(48.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{5}$ ( 105 mg , $1.00 \mathrm{mmol}, 5.0$ equiv.) and $2 \mathrm{mLCH} \mathrm{CN}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 100:0 to $85: 15$ ) affording $4 \mathrm{~d}(38.6 \mathrm{mg}, 0.112 \mathrm{mmol}, 55 \%$ for both diastereomers) as a colorless oil. The dr ( $86: 14$ ) was determined by integrating the NMR signals of ArCOCH 4.33 ppm (major), 3.90 ppm (minor). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.60-7.54$ (m, 2H, ArH), $7.49-7.43$ (m, 2H, ArH), 6.99 - 6.87 (m, 5H, ArH), 4.33 (ddd, $J=10.6,8.9,7.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 3.81 (td, $J=10.6,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCH}$ ), 2.33 (dd, $J=13.1,8.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $1.99-1.90\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.76$ (ddd, $J=13.1,7.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CHCH}_{2}$ ), $1.29\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{3}\right), 1.19\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.7$, 141.8, 133.5, 128.6, 128.3, 128.0, 126.4, 125.1 (q, J=3.8 Hz), 122.4, 51.7, 48.9, 48.5, 43.2, 38.7, 29.4, 28.5. NMR data matching literature. ${ }^{16}$

## Tert-butyl 4-benzoyl-3,3-diphenylcyclopentane-1-carboxylate (4e)



Following general procedure F, starting from $\mathbf{1 i}(49.2 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{b b}$ ( 90 mg , $0.50 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}\left(15.0 \mathrm{mg}, 0.06 \mathrm{mmol}, 0.3\right.$ equiv.) and $2 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from $100: 0$ to $85: 15$ ) affording $4 \mathrm{~d}(69.1 \mathrm{mg}, 0.162 \mathrm{mmol}, 81 \%$ yield for both diastereomers) as a colorless oil. The $\mathrm{dr}(69: 31)$ was determined by integrating the NMR signals of ArCOCH 4.85 ppm (major), 4.81 ppm (minor).

TLC: $\mathrm{R}_{\mathrm{f}}=0.28\left(\mathrm{SiO}_{2}, 90: 10\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.60-7.55(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.32$ $-7.21(\mathrm{~m}, 7 \mathrm{H}, \mathrm{ArH}), 7.01-6.95(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH}), 6.92-6.84(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH}), 4.90-4.83(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArCOCH})$, 3.27 (dd, $\left.J=13.1,10.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCO}_{2} \mathrm{tBu}\right), 2.72-2.62\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.54-2.46\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right)$,
2.42 - $2.36\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.38(\mathrm{~s}, 9 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 203.1,174.2,147.7,144.8$, 138.5, 132.3, 128.4, 128.2, 128.1, 128.0, 127.7, 126.7, 126.3, 125.9, 80.3, 60.3, 51.2, 42.5, 40.2, 31.8, 28.1. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2982 (w), 1728 (s), 1725 (s), 1685 (m), 1683 (m), 1448 (m), 1367 (m), 1225 (m), 1152 (s) HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{29} \mathrm{H}_{30} \mathrm{NaO}_{3}{ }^{+}$449.2087; Found 449.2086.
(4-Methyl-2,2-diphenylcyclopentyl)(phenyl)methanone (4f)


Following general procedure F, starting from $\mathbf{1 0}(36.7 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{5 b}$ ( 90 mg , $0.50 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}\left(15.0 \mathrm{mg}, 0.06 \mathrm{mmol}, 0.3\right.$ equiv.) and $2 \mathrm{mLCH} \mathrm{CN}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 100:0 to $\left.90: 10\right)$ affording $4 \mathrm{f}(69.1 \mathrm{mg}, 0.108 \mathrm{mmol}, 54 \%$ yield for both diastereomers) as a colorless oil. The $\mathrm{dr}(70: 30)$ was determined by integrating the NMR signals of CHMe 2.73 ppm (major) (major), 3.27 ppm (minor).

Major diastereomer TLC: $\mathrm{R}_{\mathrm{f}}=0.23\left(\mathrm{SiO}_{2}\right.$, pentane). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.64-7.57(\mathrm{~m}, 2 \mathrm{H}$, ArH), $7.45-7.36$ (m, 1H, ArH), $7.37-7.24$ (m, 6H, ArH), 7.20 (d, J=6.8 Hz, 1H, ArH), ), $7.05-6.98$ (m, 2H), $6.98-6.86(\mathrm{~m}, 2 \mathrm{H}, 3 \mathrm{H}), 4.95(\mathrm{dd}, J=9.2,3.2 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArCOCH}$ ), $2.82(\mathrm{t}, J=11.7 \mathrm{~Hz}, 1 \mathrm{H}$, MeCH), 2.46 (dt, $J=13.7,9.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $2.25\left(\mathrm{dd}, J=11.7,5.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.08-1.92(\mathrm{~m}, 1 \mathrm{H}$, $\mathrm{CH}_{2}$ ), 1.78 (ddd, $J=13.7,7.9,3.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $1.15\left(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right){ }^{13} \mathrm{C}$ NMR ( 101 MHz , $\mathrm{CDCl}_{3}$ ) $\delta 204.8,149.2,145.7,139.1,132.2,128.4,128.3,128.2,128.0,127.6,127.0,126.0,125.8$, 61.1, 52.4, 45.8, 37.6, 31.3, 20.1. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2953 (w), 1720 (s), 1681 (w), 1494 (w), 1449 (m), 1272 (s), 1110 (m), 1028 (w) HRMS (ESI/QTOF) m/z: $[\mathrm{M}+\mathrm{H}]^{+}$Calcd for $\mathrm{C}_{25} \mathrm{H}_{25} \mathrm{O}^{+} 341.1900$; Found 341.1904.

Minor diastereomer TLC $\mathrm{R}_{\mathrm{f}}=0.17\left(\mathrm{SiO}_{2}\right.$, pentane). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.79$ - $7.74(\mathrm{~m}, 2 \mathrm{H}$, ArH), 7.50 - 7.44 (m, 1H, ArH), $7.44-7.39$ (m, 2H, ArH), 7.36 (t, $J=7.7 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), 7.28 (d, J=7.5 Hz, 2H, ArH), 7.18-7.12 (m, 1H, ArH), 7.09-7.00 (m, 4H, ArH), 6.99-6.93 (m, 1H, ArH), 4.90 (dd, J $=7.9,2.4 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArCOCH}$ ), $3.27\left(\mathrm{dd}, J=13.1,10.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}\right.$ ), 2.61 (td, $J=8.9,6.1 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CH}_{2}$ ), 2.31 (dd, $J=13.1,5.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.22 (ddd, $J=13.3,8.4,2.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $1.87-1.78(\mathrm{~m}$, $1 \mathrm{H}, \mathrm{CH}_{2}$ ), $0.95\left(\mathrm{~d}, \mathrm{~J}=7.0 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 202.5,149.3,147.2,138.4,132.5$, 128.5, 128.4, 128.2, 128.1, 127.8, 127.2, 125.9, 125.6, 60.1, 55.1, 46.3, 38.4, 31.7, 22.0. HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{25} \mathrm{H}_{24} \mathrm{NaO}^{+}$363.1719; Found 363.1730.

## (2,2-diphenyl-4-(trifluoromethyl)cyclopentyl)(phenyl)methanone (4g)



Following general procedure F, starting from $\mathbf{1 k}(21.4 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{b}$ ( 45 mg , $0.25 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}\left(7.5 \mathrm{mg}, 0.030 \mathrm{mmol}, 0.3\right.$ equiv.) and $2 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 72 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 100:0 to $90: 10$ ) affording $4 \mathrm{~g}(35.1 \mathrm{mg}, 89.1 \mu \mathrm{~mol}, 89 \%$ yield for both diastereomers) as a colorless oil as mixture of two diastereomers. The $\mathrm{dr}(61: 39)$ was determined by integrating the NMR signals of ArCOCH 5.04 ppm (major), 5.06 ppm (minor). NMR reported for major diastereomer.

TLC: $\mathrm{R}_{\mathrm{f}}=0.51\left(\mathrm{SiO}_{2}, 8: 1\right.$ pentane:Et $\left.\mathrm{t}_{2} \mathrm{O}\right)$. Major diastereomer: ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.66-7.60$ (m, 2H, ArH), $7.47-7.38(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH}), 7.35-7.28(\mathrm{~m}, 4 \mathrm{H}, \mathrm{ArH}), 7.09(\mathrm{~d}, \mathrm{~J}=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.03-6.92$ (m, 5H, ArH), $5.04\left(\mathrm{~d}, \mathrm{~J}=2.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}\right.$ ), $3.41-3.35\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCF}_{3}\right), 2.56-2.26\left(\mathrm{~m}, 4 \mathrm{H}, \mathrm{CH}_{2}\right)$. ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 202.8,147.0,143.8,138.3,132.5,128.7,128.1$ (q, $J=277.8 \mathrm{~Hz}$ ), 128.2, 128.0, 127.9, 127.7, 126.7, 126.6, 126.2, 60.1, 50.0, 40.9 (q, $J=28.2 H z), 37.2(\mathrm{~d}, J=2.1 \mathrm{~Hz}), 28.8(\mathrm{~d}$, $J=2.3 \mathrm{~Hz}) .{ }^{19}$ F NMR (376 MHz, CDCl ${ }_{3}$ ) $\delta$-69.8. IR ( $\mathrm{v}_{\mathrm{max}}, \mathrm{cm}^{-1}$ ) 3061 (w), 2953 (w), 1680 (m), 1597 (w), 1447 (m), 1275 (m), 1220 (m), 1152 (s), 1116 (s). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{25} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{NaO}^{+}$417.1437; Found 417.1441.

## (2,2-Diphenylcyclopentyl)(phenyl)methanone (4h)



Following general procedure F, starting from $\mathbf{1 p}(29.2 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{5 b}$ ( 90 mg , $0.50 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}(15.0 \mathrm{mg}, 60.0 \mu \mathrm{~mol}, 0.3$ equiv.) and 2 mL CH 3 CN the reaction mixture was stirred for 72 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 100:0 to $95: 5$ ) affording $\mathbf{4 h}(14.3 \mathrm{mg}, 43.8 \mu \mathrm{~mol}, 22 \%$ ) as pale yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.72-7.66(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.47-7.41(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.36-7.26(\mathrm{~m}, 6 \mathrm{H}$, ArH), $7.20-7.14$ (m, 1H, ArH), $7.08-7.02$ (m, 2H, ArH), $7.02-6.89$ (m, 3H, ArH), 4.85 (dq, J = 8.4, $1.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}), 3.14-3.00\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right)$, $2.36\left(\mathrm{dd}, J=12.2,7.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.28-2.16(\mathrm{~m}$, 1H, CH2), 2.16-2.05 (m, 1H, CH2), 2.03-1.91 (m, 1H, CH2), 1.71-1.58 (m, 1H, CH2). ${ }^{13} \mathrm{C}$ NMR ( 101 $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 204.1,148.6,146.0,138.7,132.4,128.4,128.3,128.3,128.1,127.7,127.0,126.0$, 125.8, 60.8, 52.7, 36.9, 29.2, 22.6. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $\mathrm{C}_{24} \mathrm{H}_{23} \mathrm{O}^{+} 327.1743$; Found 327.1748. Data matching reported value. ${ }^{17}$

## Dimethyl 4-benzoyl-3,3-diphenylcyclopentane-1,1-dicarboxylate (4i)



Following general procedure E, starting from $\mathbf{1 b}$ ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and 5 b ( 54.1 mg , $0.300 \mathrm{mmol}, 1.5$ equiv.) and $2 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 95:5 to $80: 20$ ) affording $4 \mathbf{i}(74.3 \mathrm{mg}, 0.168 \mathrm{mmol}, 84 \%)$ as white solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.18\left(\mathrm{SiO}_{2}, 90: 10\right.$ pentane:EtOAc). Mp: $149-151^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.61-7.57$ (m, 2H, ArH), 7.38-7.32 (m, 3H, ArH), 7.28-7.22 (m, 4H, ArH), 7.17-7.11 (m, 1H, ArH), 7.01-6.97 (m, 2H, ArH), 6.93-6.88 (m, 2H, ArH), 6.86-6.81 (m, 1H, ArH), 5.03 (dt, J = 8.0, $1.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 3.84$ (d, J = $13.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{Ph}_{2} \mathrm{CCHCH}_{2}$ ), $3.73\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.26\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.25(\mathrm{~d}, \mathrm{~J}=13.5 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{Ph}_{2} \mathrm{CCHCH}_{2}$ ), $3.14\left(\mathrm{dd}, \mathrm{J}=14.7,8.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.70\left(\mathrm{dd}, \mathrm{J}=14.7,2.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 202.8,171.9,171.6,145.6,144.3,138.2,132.5,128.34,128.3,128.1,127.88$, $127.82,127.5,126.6,126.2,59.5,59.5,53.3,52.8,51.7,43.9,36.1$. HRMS (ESI/QTOF) m/z: $[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{28} \mathrm{H}_{26} \mathrm{NaO}_{5}{ }^{+} 465.1672$; Found 465.1669. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2952 (w), 2258 (w), 1734 (s), 1676 (m), 1597 (w), 1495 (w), 1447 (m), 1258 (s), 1220 (s), 911 (m).


Following general procedure E, starting from 1b ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{c}$ ( 35 mg , $0.50 \mathrm{mmol}, 2.5$ equiv.), (PhO) ${ }_{2} \mathrm{PO}_{2} \mathrm{H}\left(15.0 \mathrm{mg}, 60.0 \mu \mathrm{~mol}, 0.3\right.$ equiv.) and $2 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to 60:40) affording 4 j ( $51.2 \mathrm{mg}, 0.154 \mathrm{mmol}, 77 \%$ yield for both diastereomers) as a colorless oil. The $\mathrm{dr}(57: 43)$ was determined by integrating the NMR signals of $\mathrm{CH}_{3} \mathrm{COCH} 3.23 \mathrm{ppm}$ (major), 3.69 ppm (minor).
(4j1) major TLC: $\mathrm{R}_{\mathrm{f}}=0.11\left(\mathrm{SiO}_{2}, 2: 1\right.$ pentane:Et $\left.{ }_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR (400 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 7.91$ - $7.86(\mathrm{~m}, 2 \mathrm{H}$, ArH), $7.60-7.53(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.51-7.44(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 4.24$ (ddd, J=8.7, 7.6, 6.3 Hz, 1H, ArCOCH), $3.77\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.70\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.23\left(\mathrm{dt}, J=9.7,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{COCH}\right), 2.82-2.67(\mathrm{~m}, 3 \mathrm{H}$, $\mathrm{CH}_{2}$ ), $2.63\left(\mathrm{dd}, \mathrm{J}=14.2,6.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.12\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{COCH}_{3}\right) .{ }^{13} \mathrm{C} \mathbf{N M R}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 207.8$, 200.1, 172.8, 171.3, 136.3, 133.4, 128.8, 128.6, 59.4, 54.5, 53.3, 53.1, 49.0, 37.3, 36.3, 29.6. IR (v $\mathrm{max}^{2}$, $\mathrm{cm}^{-1}$ ) 2954 (w), 1732 (s), 1710 (s), 1680 (s), 1599 (w), 1580 (w), 1435 (m), 1361 (m), 1250 (s), 1165 (s). HRMS (ESI/QTOF) m/z: [M + H $]^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{O}_{6}{ }^{+} 333.1333$; Found 333.1334.
(4j2) minor TLC: $\mathrm{R}_{\mathrm{f}}=0.22\left(\mathrm{SiO}_{2}, 2: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ס $8.01-7.91(\mathrm{~m}, 2 \mathrm{H}$, ArH), $7.63-7.54(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}$ ), $7.52-7.45(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 4.25(\mathrm{td}, J=8.9,7.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}), 3.76$ (s, 3H, OCH3), 3.72 (s, 3H, OCH3), 3.69 (dd, J=9.0, $8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{COCH}$ ), 2.84 (ddd, $J=13.5,11.3$, $\left.9.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.43-2.25\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.19\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{COCH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 207.8$, 199.6, 171.6, 171.3, 136.1, 133.6, 128.9, 128.8, 60.0, 53.2, 53.2, 53.0, 47.7, 38.4, 36.6, 29.4. IR (v $\mathrm{v}_{\text {max }}$, $\mathrm{cm}^{-1}$ ) 2956 (w), 1735 (s), 1713 (s), 1685 (m), 1597 (w), 1449 (m), 1360 (m), 1262 (s), 1207 (m), 1176 (m). HRMS (ESI/QTOF) m/z: [M + H] ${ }^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{O}_{6}{ }^{+}$333.1333; Found 333.1335.

## Trimethyl 4-benzoylcyclopentane-1,1,3-tricarboxylate (4k)



Following general procedure F, starting from 1b ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{d}$ ( 43 mg , $0.50 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}\left(15.0 \mathrm{mg}, 60.0 \mu \mathrm{~mol}, 0.3\right.$ equiv.) and $2 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from $80: 20$ to $60: 40$ ) affording $4 \mathbf{k}(40.4 \mathrm{mg}, 0.116 \mathrm{mmol}, 58 \%$ yield for both diastereomers) as a colorless oil. The dr (53:47) was determined by integrating the NMR signals of ArH 7.90 ppm (major), 7.99 ppm (minor).
(4k1) TLC: $\mathrm{R}_{\mathrm{f}}=0.31\left(\mathrm{SiO}_{2}, 2: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.03-7.94(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.61-7.55$ (m, 1H, ArH), $7.52-7.43$ (m, 2H, ArH), 4.25 (q, J = $8.8 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArCOCH}$ ), 3.77 (s, 3H, $\mathrm{OCH}_{3}$ ), $3.72\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.63\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.58(\mathrm{t}, \mathrm{J}=8.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{MeOCOCH}$ ), 2.86 (ddd, $J=$ $14.0,8.9,6.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.51 (dd, $J=13.8,8.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.29 (dd, $J=13.6,9.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 199.2,174.1,171.9,171.2,136.2,133.6,128.9,128.8,59.9,53.2,53.1$, 52.3, 49.0, 45.3, 38.5, 36.9. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2955 (w), 1734 (s), 1685 (m), 1597 (w), 1437 (m), 1260 ( s ), 1205 (s), 1173 (m), 1018 (w). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{20} \mathrm{NaO}_{7}^{+}$371.1101; Found 371.1105.
(4k2) TLC: $\mathrm{R}_{\mathrm{f}}=0.19\left(\mathrm{SiO}_{2}, 2: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.94-7.87(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.61-7.53(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.51-7.43(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 4.23(\mathrm{td}, \mathrm{J}=8.1,6.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 3.76 (s, 3H, $\mathrm{OCH}_{3}$ ), $3.72\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.50\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), 3.28 (dt, $J=9.6,7.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{MeOCOCH}$ ), 2.81 (dd, J $\left.=13.9,9.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.74-2.62\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C} \operatorname{NMR}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ б 199.6, 173.0, 172.8, 171.3, 136.3, 133.4, 128.8, 128.6, 59.2, 53.3, 53.0, 51.9, 48.0, 46.7, 37.1, 36.3. IR ( $\left.\mathrm{v}_{\max } \mathrm{cm}^{-1}\right) 2955$ (w), 1732 (s), 1685 (m), 1597 (w), 1448 (m), 1436 (m), 1363 (m), 1255 (s), 1207 (s), 1204 (s), 1169 (m).

HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{20} \mathrm{NaO}_{7}{ }^{+} 371.1101$; Found 371.1100.

## Dimethyl 3-benzoyl-4-(trimethylsilyl)cyclopentane-1,1-dicarboxylate (4I)



Following general procedure F, starting from 1b ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathrm{e}(50 \mathrm{mg}$, $0.50 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}(15.0 \mathrm{mg}, 60.0 \mu \mathrm{~mol}, 0.3$ equiv.) and 2 mL CH 3 CN the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 90:20 to 80:20) affording $4 \mathrm{II}(31.1 \mathrm{mg}, 85.9 \mu \mathrm{~mol}, 43 \%$ yield for both diastereomers) as a colorless oil. Due to overlapping of signal, the $\mathrm{dr}(55: 45)$ was determined by integrating the NMR signals of $\mathrm{CH}_{2} 2.27 \mathrm{ppm}$ (major), 4.08 ppm for ArCOCH (minor).

TLC: $\mathrm{R}_{\mathrm{f}}=0.36\left(\mathrm{SiO}_{2}, 5: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right)$.
Minor diastereomer ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.02$ - 7.90 ( $\mathrm{m}, 2 \mathrm{H}, \mathrm{ArH}$, in both diastereomers), 7.58 (td, $J=7.4,4.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ in both diastereomers), 7.47 (q, $J=7.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ in both diastereomers), 4.08 (td, J= 8.2, 5.5 Hz, 1H, ArCOCH), $3.76-3.75\left(\mathrm{~m}, 6 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), 2.67 (dd, $J=13.9,8.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH} 2$ ), $2.54-2.38\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{CH}_{2}\right), 1.51\left(\mathrm{dt}, J=11.9,8.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{Me}_{3} \mathrm{SiCH}\right), 0.0\left(\mathrm{~s}, 9 \mathrm{H}, \mathrm{SiCH}_{3}\right)$.

Major diastereomer. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.02$ - 7.90 ( $\mathrm{m}, 2 \mathrm{H}, \mathrm{ArH}$, in both diastereomers), 7.58 (td, $J=7.4,4.6 \mathrm{~Hz}, 1 \mathrm{H}$, ArH in both diastereomers), 7.47 ( $\mathrm{q}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}$, ArH in both diastereomers), $3.71\left(\mathrm{~s}, 7 \mathrm{H}, 2 \mathrm{OCH}_{3}\right.$ and ArCOCH$), 2.80-2.68\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.27\left(\mathrm{dd}, J=13.3,8.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right)$, 2.05-1.92 (m, 2H, , CH 2 and $\mathrm{Me}_{3} \mathrm{SiCH}$ ), $0.0\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{SiCH}_{3}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) for both diastereomer $\delta 202.7,201.0,173.3,172.9,172.2,172.0,137.0$, 136.9, 133.3 (for 2 diastereomers), 128.9, 128.8, 128.7, 128.5, 61.4, 61.3, 53.0, 53.0, 52.9, 52.9, 48.5, $47.5,41.8,39.9,37.2,37.1,31.4,28.1,-1.1,-2.7$.

IR ( $\mathrm{V}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2953 (m), 1733 (s), 1684 (m), 1597 (w), 1436 (m), 1249 (s), 1200 (s), 1162 (m), 1098 (m), 1006 (m), 837 (s) HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{19} \mathrm{H}_{26} \mathrm{NaO}_{5} \mathrm{Si}^{+} 385.1442$; Found 385.1449 .

## Dimethyl 4-benzoyl-3,3-diethylcyclopentane-1,1-dicarboxylate (4m)



Following general procedure $F$, starting from $\mathbf{1 b}(52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{f}(42 \mathrm{mg}$, $0.50 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}$ ( $15.0 \mathrm{mg}, 60.0 \mu \mathrm{~mol}, 0.3$ equiv.) and $2 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage
$\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 95:5 to $80: 20$ ) affording 4 m ( $47.7 \mathrm{mg}, 0.138 \mathrm{mmol}, 69 \%$ ) pale yellow oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.22\left(\mathrm{SiO}_{2}, 5: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.95-7.85(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.61$ $7.51(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.45(\mathrm{dd}, J=8.4,7.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 3.86(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}), 3.78(\mathrm{~s}, 3 \mathrm{H}$, $\mathrm{OCH}_{3}$ ), $3.75\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.70\left(\mathrm{qd}, \mathrm{J}=14.1,7.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{COCHCH}_{2}\right), 2.59\left(\mathrm{~d}, \mathrm{~J}=14.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right.$ ), 2.14 (d, $J=14.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 1.50 (dq, $J=14.7,7.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}$ ), 1.37 (ttd, $J=14.7,7.3,2.4 \mathrm{~Hz}$, $2 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}$ ), 1.26 (dq, $J=14.8,7.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}$ ), $0.82\left(\mathrm{t}, J=7.4 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{3}\right.$ ), $0.68(\mathrm{t}, \mathrm{J}=7.4$ $\mathrm{Hz}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{3}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 202.8, 173.7, 172.5, 138.8, 133.0, 128.7, 128.4, 58.7, 53.1, 53.0, 52.2, 51.2, 44.0, 36.9, 29.4, 26.7, 9.1, 9.0. IR ( $\mathrm{v}_{\max } \mathrm{cm}^{-1}$ ) 2965 (m), 2963 (m), 2881 (w), 1734 (s), 1675 (m), 1596 ( w ), 1447 (m), 1255 ( s$), 1202$ (m), 1079 (m). HRMS (ESI/QTOF) m/z: [M + $\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{26} \mathrm{NaO}_{5}{ }^{+}$369.1672; Found 369.1669.

Dimethyl 4-benzoyl-3-methyl-3-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (4n)


Following general procedure F, starting from 1b ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and 5 g ( 42.0 mg , $500 \mu \mathrm{~mol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}\left(15.0 \mathrm{mg}, 60.0 \mu \mathrm{~mol}, 0.3\right.$ equiv.) and $2 \mathrm{~mL} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 95:5 to $80: 20$ ) affording $\mathbf{4 n}(48.8 \mathrm{mg}, 0.142 \mathrm{mmol}, 71 \%$ ) as a pale yellow oil. The $\operatorname{dr}(77: 23)$ was determined by integrating the NMR signals of ArCOCH .
(4n1) Major TLC: $\mathrm{R}_{\mathrm{f}}=0.32\left(\mathrm{SiO}_{2}, 5: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.88-7.79(\mathrm{~m}, 2 \mathrm{H}$, ArH), $7.57-7.48(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.42 (dd, $J=8.4,7.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 4.72-4.61$ (m, 2H, CH3CCH2), 4.09 (dd, $J=10.6,7.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), $3.77\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.76\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), 2.77 (dd, $J=13.9,10.6$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $2.67\left(\mathrm{dd}, J=13.9,7.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right.$ ), $2.56\left(\mathrm{~d}, J=14.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.47(\mathrm{~d}, \mathrm{~J}=14.3 \mathrm{~Hz}$, $\left.1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.75\left(\mathrm{~d}, J=1.3 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CCH}_{3}\right), 1.10\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CHCCH}_{3}\right) .{ }^{13} \mathrm{C} \mathrm{NMR}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 201.2, 173.4, 172.3, 148.6, 138.5, 133.0, 128.6, 128.3, 111.9, 58.0, 53.1, 53.1, 51.9, 51.6, 46.2, 36.9, 22.3, 20.2. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2955 (w), 1733 (s), 1678 (m), 1437 (m), 1379 (w), 1253 (s), 1205 (m), 1173 (m), $900(\mathrm{w})$. HRMS (ESI/QTOF) m/z: [M + H] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{25} \mathrm{O}_{5}{ }^{+}$345.1697; Found 345.1699.
(4n2) Minor. TLC: $\mathrm{R}_{\mathrm{f}}=0.24\left(\mathrm{SiO}_{2}, 5: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.91-7.84(\mathrm{~m}, 2 \mathrm{H}$, ArH), $7.59-7.50(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.44 (dd, $J=8.4,6.9 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 4.74-4.66\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CCH}_{2}\right), 3.85$ (dd, $J=7.5,3.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 3.76 (s, 3H, OCH ${ }_{3}$ ), 3.73 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}_{3}$ ), 3.21 (d, J=13.9 Hz, 1H, $\mathrm{CH}_{2}$ ), $2.84-2.72\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.43\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.56\left(\mathrm{~d}, \mathrm{~J}=1.3 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CCH}_{3}\right), 1.25(\mathrm{~s}, 3 \mathrm{H}$, $\mathrm{CHCCH}_{3}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 201.6, 173.5, 172.1, 149.3, 137.7, 132.9, 128.7, 128.4, 111.2, $59.5,54.4,53.2,53.1,52.8,44.4,36.6,28.3,21.2$. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2955 (w), 1736 (s), 1682 (m), 1446 (m), 1364 (w), 1256 (s), 1210 (m), 1004 (w). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{NaO}_{5}{ }^{+}$367.1516; Found 367.1521.

## Dimethyl 3-benzoyl-4-(2-oxopyrrolidin-1-yl)cyclopentane-1,1-dicarboxylate (40)



Following general procedure E, starting from $\mathbf{1 b}(52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and 5 h ( 33.3 mg , $0.300 \mathrm{mmol}, 1.5$ equiv.) and $2 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 25:75 to $15: 85$ ) affording $40(61.9 \mathrm{mg}, 0.166 \mathrm{mmol}, 83 \%$ for both diastereoisomers) as colorless oil. The product was isolated as a mixture of 2 diastereomers. The diastereomeric ratio (80:20) was determined by integrations of the NMR signals of $\mathrm{NCHCH}_{2}$ in the crude mixture 4.99 ppm (major), 4.46 ppm (minor). The NMR data is reported for the major diastereoisomer only.

TLC: $\mathrm{R}_{\mathrm{f}}=0.33\left(\mathrm{SiO}_{2}, 20: 80\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.99-7.94(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7.57-7.52 (m, 1H, ArH), 7.51-7.45 (m, 2H, ArH), $4.99(\mathrm{ddd}, \mathrm{J}=11.0,9.1,7.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{NCHCH}$ ) , 4.37 $-4.27(\mathrm{~m}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.78\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.20\left(\mathrm{dt}, \mathrm{J}=9.4,7.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{NCH}_{2}\right)$, 3.01 (td, $J=9.0,4.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}_{2}$ ), 2.88-2.79 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.62-2.55 (m, 2H, CH2), 2.48 (ddd, $J$ $=13.5,7.5,1.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH} 2$ ), 2.10 (ddd, $J=17.0,9.4,7.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $1.77-1.64\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 200.7,175.4,172.3,171.6,136.6,133.8,128.7,128.6,57.8,53.8,53.3,53.2$, 46.9, 44.7, 35.4, 34.8, 30.7, 18.1. HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{23} \mathrm{NNaO}_{6}{ }^{+} 396.1418$; Found 396.1427. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2955 (w), 1732 (s), 1677 ( s$), 1423$ (m), 1264 (s), 1203 ( s$), 1164$ (m).

## Dimethyl 3-benzoyl-4-(1,3-dioxoisoindolin-2-yl)cyclopentane-1,1-dicarboxylate (4p)



Following general procedure E, starting from $\mathbf{1 b}(52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{i}(51.9 \mathrm{mg}$, $0.300 \mathrm{mmol}, 1.5$ equiv.) and $2 \mathrm{mLCH} \mathrm{CN}_{3} \mathrm{CN}$ the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 30:70 to $50: 50$ ) affording 4 p ( $47.9 \mathrm{mg}, 0.110 \mathrm{mmol}, 55 \%$ for both diastereomers) as sticky oil. The diastereomeric ratio (75:25) was determined by integrations of the NMR signals of C(O)CH. 4.24 ppm (major), 4.77 (minor) in the crude mixture.

## 2p1 major

TLC: $\mathrm{R}_{\mathrm{f}}=0.43\left(\mathrm{SiO}_{2}, 60: 40\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $\left.400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.72-7.65(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.61-7.51(\mathrm{~m}, 4 \mathrm{H}, \mathrm{ArH}), 7.35-7.28(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.24-7.18(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 5.23(\mathrm{td}, \mathrm{J}=9.0,7.2 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{NCHCH}_{2}$ ), 4.24 (ddd, $J=11.2,9.5,7.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.80\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.77\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.28$ (dd, $J=13.6,11.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 3.08 (dd, $J=14.3,7.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.75 (ddd, $J=14.4,8.7,1.2 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.52 (ddd, $J=13.7,7.0,1.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 198.0,173.1,171.2$, 167.8, 136.9, 134.0, 133.1, 131.4, 128.6, 128.2, 123.2, 58.8, 53.3, 53.1, 51.3, 49.3, 36.5, 35.8. IR ( $\mathrm{v}_{\text {max }}$, $\mathrm{cm}^{-1}$ ) 2955 (w), 1731 (s), 1714 (s), 1684 (m), 1598 (w), 1437 (w), 1375 (m), 1253 (m), 914 (w), 726 (m).
HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{21} \mathrm{NNaO}_{7}^{+}$458.1210; Found 458.1209.

## 2p2 minor

TLC: $\mathrm{R}_{\mathrm{f}}=0.50\left(\mathrm{SiO}_{2}, 60: 40\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.93-7.87(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.76$ (dt, $J=7.1,3.6 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $7.68(\mathrm{tt}, J=9.3,3.6 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 77.50-7.43(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.36(\mathrm{t}, J=$ $7.7 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), 5.24 (q, $J=9.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{NCHCH}$ ), 4.77 (td, $J=10.1,8.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 3.86 (s, $3 \mathrm{H}, \mathrm{CH}_{3}$ ), 3.76 (s, 3H, CH3), 3.09 (dd, $J=13.5,8.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.98 (dd, $J=13.7,9.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.77 (dd, $J=13.7,9.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.31 (dd, $J=13.5,10.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 198.6,171.8,171.4,167.9,136.4,134.2,133.5,131.8,128.8,128.6,123.4,58.0,53.4,53.3,51.0$,

## Dimethyl 3-benzoyl-4-(thiophen-2-yl)cyclopentane-1,1-dicarboxylate (4q)



Following general procedure F, starting from 1b ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{j}$ ( 55 mg , $0.50 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}\left(15.0 \mathrm{mg}, 60.0 \mu \mathrm{~mol}, 0.3\right.$ equiv.) and $2 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 90:10 to 80:20) obtained $4 \mathbf{q}(36.5 \mathrm{mg}, 98.1 \mu \mathrm{~mol}, 49 \%$ ) as pale yellow oil mixture of 2 diastereomers. The $\mathrm{dr}(68: 32)$ was determined by integrating the crude NMR signals of ArCOCH .
TLC: $\mathrm{R}_{\mathrm{f}}=0.4\left(\mathrm{SiO}_{2}, 4: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right)$. NMR reported for major diastereomer ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 7.92-7.82(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.58-7.50(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.42(\mathrm{dd}, J=8.4,7.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.08$ (dd, $J=5.0,1.3 \mathrm{~Hz}, 1 \mathrm{H}$, Thiophene H), $6.88-6.77$ (m, 2H, Thiophene H), 4.10 (ddd, $J=11.4,10.4$, $7.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 3.99 (td, J = 9.8, $8.5 \mathrm{~Hz}, 1 \mathrm{H}$, ThiopheneCH), 3.79 (s, 3H, OCH3), 3.77 (s, 3H, $\mathrm{OCH}_{3}$ ), 3.09 (dd, $J=13.6,7.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.95 (dd, $J=13.8,8.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}$ ), 2.43 (ddd, $J=13.6$, $\left.10.3,5.6 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.8,172.5,171.8,145.5,136.7,133.5,128.8$, 128.6, 126.9, 124.5, 123.6, 59.2, 54.7, 53.2, 53.2, 42.8, 42.4, 39.1. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2953 (w), 1732 (s), 1681 (m), 1597 (w), 1436 (m), 1256 (s), 1204 (m), 1166 (m), 1101 (m). HRMS (ESI/QTOF) m/z: [M + $\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{20} \mathrm{NaO}_{5} \mathrm{~S}^{+} 395.0924$; Found 395.0922.

## Dimethyl 3-(benzofuran-2-yl)-4-benzoylcyclopentane-1,1-dicarboxylate (4r)



Following general procedure F, starting from 1b ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{k}$ ( 72 mg , $0.50 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}\left(15.0 \mathrm{mg}, 60.0 \mu \mathrm{~mol}, 0.3\right.$ equiv.) and $2 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 90:10 to $80: 20$ ) obtained 4 r ( $21.1 \mathrm{mg}, 51.9 \mu \mathrm{~mol}, 26 \%$ ) as off-white amorphous solid. The $\mathrm{dr}(81: 19)$ was determined by integrating the crude NMR signals of ArCOCH.
TLC: $\mathrm{R}_{\mathrm{f}}=0.37\left(\mathrm{SiO}_{2}, 4: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right)$. NMR reported for major diastereomer only ${ }^{1} \mathrm{H}$ NMR $(600 \mathrm{MHz}$, $\mathrm{CDCl}_{3}$ ) $\quad 7.92-7.88$ (m, 2H, ArH), $7.52-7.50(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.42-7.39$ (m, 2H, ArH), $7.39-7.34$ (m, $2 \mathrm{H}, \mathrm{ArH}$ ), $7.20-7.17$ (m, 1H, ArH), $7.14(\mathrm{td}, J=7.5,1.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), $6.41(\mathrm{t}, J=0.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCCH}$ benzofurane), 4.24 (q, J=9.1 Hz, 1H, ArCOCH), 4.06-3.99 (m, 1H, ArCOCHCH), $3.79\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, 3.78 (s, 3H, OCH 3 ), $3.06-2.96\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.61\left(\mathrm{dd}, J=13.7,10.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right.$ ), 2.47 (dd, J=13.7, $\left.9.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right){ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 199.4,172.3,171.7,157.9,154.9,136.5,133.5,128.9$,
128.8, 128.7, 123.8, 122.8, 120.7, 111.0, 103.1, 59.6, 53.2, 53.2, 51.1, 41.3, 39.0, 38.9. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 3044 (w), 2954 (w), 1736 (s), 1685 (m), 1599 (w), 1454 (s), 1254 (s), 1214 (m), 1182 (m), 809 (m). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{22} \mathrm{NaO}_{6}{ }^{+}$429.1309; Found 429.1305.

## Dimethyl 8-benzoylspiro[3.4]octane-6,6-dicarboxylate (4s)



Following general procedure F, starting from $\mathbf{1 b}$ ( $52.4 \mathrm{mg}, 0.200 \mathrm{mmol}, 1.0$ equiv.) and $5 \mathbf{5 l}$ ( 34 mg , $0.50 \mathrm{mmol}, 2.5$ equiv.), ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}\left(\left(15.0 \mathrm{mg}, 60.0 \mu \mathrm{~mol}, 0.3\right.\right.$ equiv.) and $2 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 90:10 to 80:20) obtained $\mathbf{4 s}(32.3 \mathrm{mg}, 97.8 \mu \mathrm{~mol}, 49 \%$ ) as colorless oil with recovered starting material 1b ( $52.4 \mathrm{mg}, 97.1 \mu \mathrm{~mol}, 49 \%$ )
TLC: $\mathrm{R}_{\mathrm{f}}=0.24\left(\mathrm{SiO}_{2}, 5: 1\right.$ pentane:Et $\left.{ }_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.99(\mathrm{dd}, J=7.6,1.6 \mathrm{~Hz}, 2 \mathrm{H}$, ArH), 7.58 (t, $J=7.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.49 (t, $J=7.6 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $3.91(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOH}), 3.75$ (s, 3H, OCH $H_{3}$, $3.74\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.78\left(\mathrm{~d}, \mathrm{~J}=13.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{COCHCCH}_{2}\right), 2.67-2.52(\mathrm{~m}, 2 \mathrm{H}$, , ArCOCHCH 2 ), $2.45\left(\mathrm{~d}, \mathrm{~J}=13.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{COCHCH}_{2}\right), 2.04-1.86(\mathrm{~m}, 3 \mathrm{H}$, cyclobutyl $H$ ), $1.85-1.71(\mathrm{~m}$, 2 H , cyclobutyl $H$ ), $1.57-1.50\left(\mathrm{~m}, 1 \mathrm{H}\right.$, cyclobutyl $H$ ). ${ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 201.4,173.3,172.3$, 138.1, 133.3, 128.8, 128.6, 58.4, 53.3, 53.0, 52.9, 50.2, 47.0, 36.6, 33.8, 29.7, 16.3. IR ( $\left.\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}\right) 2955$ (m), 1733 (s), 1676 (m), 1596 (w), 1435 (m), 1254 (s), 1198 (s), 1094 (m), 1002 (m). HRMS (ESI/QTOF) $\mathrm{m} / \mathrm{z}:[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{19} \mathrm{H}_{22} \mathrm{NaO}_{5}{ }^{+}$353.1359; Found 353.1364.
(6-(Naphthalen-1-yl)-3,3a,4,5-tetrahydro-1H-cyclopenta[c]furan-5-yl)(phenyl)methanone (7a)


Following general procedure F , starting from $\mathbf{6 a}(34.0 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0 \text { equiv.) and ( } \mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}$ ( $7.5 \mathrm{mg}, 30 \mu \mathrm{~mol}, 0.3$ equiv.) and $2 \mathrm{mLCH} \mathrm{CN}_{3} \mathrm{CN}$ the reaction mixture was stirred for 72 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 90:10 to $80: 20$ ) obtained $\mathbf{7 a}(15.6 \mathrm{mg}, 46.0 \mu \mathrm{~mol}, 46 \%$ ) as colorless oil and $\mathbf{6 a}(16.9 \mathrm{mg}, 49.6 \mu \mathrm{~mol}$, $50 \%$ ) was recovered. The dr (68:32) was determined by integrating the crude NMR signals of ArCOCH. 5.66 ppm (major - cis), 5.32 ppm (minor trans) based on reported data. ${ }^{10 \mathrm{~b}}$
TLC: $\mathrm{R}_{\mathrm{f}}=0.16\left(\mathrm{SiO}_{2}, 5: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right)$.
Major diastereomer. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.99(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 7.62(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}$, ArH), 7.59 (d, J=7.9 Hz, 1H, ArH), $7.53-7.49(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.47-7.43(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.32-7.29(\mathrm{~m}$, $1 \mathrm{H}, \mathrm{ArH}$ ), $7.26-7.18$ (m, 3H, ArH), 7.14 (t, $J=7.7 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $5.68-5.63$ (m, 1H, ArCOCH), $4.30-$ $4.20\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{OCH}_{2}\right), 4.07\left(\mathrm{ddd}, J=13.7,4.0,1.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}\right), 3.70\left(\mathrm{q}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}\right), 3.56$ (dd, J=10.2, $8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCHCH}_{2} \mathrm{CH}$ ), 2.56-2.45 (m, 1H, CH2), 2.39-2.37 (m, 1H, CH2).

Minor diastereomer. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.01$ ( $\mathrm{d}, J=8.8 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), 7.82 (d, $J=8.0,1 \mathrm{H}$, ArH), 7.76-7.71 (m, 2H, ArH), $7.70-7.67$ (m, 2H, ArH), $7.54-7.48$ (m, 1H, ArH) $7.47-7.43$ (m, 1H, ArH) $7.39-7.28$ (m, 2H, ArH), $7.24-7.20(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 5.32(\mathrm{~d}, \mathrm{~J}=9.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}), 4.24-4.19$
(m, 2H, OCH2), $3.96-3.86\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{OCH}_{2}\right), 3.41\left(\mathrm{dd}, J=10.0,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{COCH}_{2} \mathrm{CH}\right.$ ), $2.60(\mathrm{dd}, J=$ $\left.12.5,6.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.39-2.33\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) (presented as a mixture of diastereomers) $\delta 200.5,200.2,152.3,150.8$, $137.2,136.3,133.79,133.76,133.63,133.61,133.0,132.8,131.3,131.1,130.6,130.3,128.6,128.5$, 128.4, 128.3, 128.2, 128.1, 127.7, 126.5, 126.3, 126.2, 126.0, 125.89, 125.86, 125.7, 125.3, 125.19, $125.16,73.2,72.6,64.9,64.3,64.1,63.4,52.0,51.7,33.8,33.2$. Data matching reported value. ${ }^{10 \mathrm{~b}}$

HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{20} \mathrm{NaO}_{2}{ }^{+}$363.1356; Found 363.1355.

## Phenyl(4-phenylhexahydro-1H-cyclopenta[c]furan-5-yl)methanone (7b)



Following general procedure F , starting from $\mathbf{6 b}(29.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0 \text { equiv.) and ( } \mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}$ ( $7.5 \mathrm{mg}, 30 \mu \mathrm{~mol}, 0.3$ equiv.) and $2 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ the reaction mixture was stirred for 72 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to 60:40) obtained 7b ( $19.6 \mathrm{mg}, 67.1 \mu \mathrm{~mol}, 67 \%$ for four diastereomers) as colorless oil. Due to complicated NMR crude mixture, the $\mathrm{dr}(15: 18: 30: 37)$ was determined by the isolated yield of the four diastereomers.

7 b1 ( $2.90 \mathrm{mg}, 9.93 \mu \mathrm{~mol}, 10 \%$ yield). TLC: $\mathrm{R}_{\mathrm{f}}=0.17\left(\mathrm{SiO}_{2}, 3: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathbf{H}$ NMR ( 400 MHz , $\mathrm{CDCl}_{3}$ ) $\delta 7.56$ - 7.49 (m, 2H, ArH), 7.35 (td, J=7.6, $2.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), $7.24-7.17$ (m, 2H, ArH), $7.02-$ 6.92 (m, 5H, ArH), $5.00-4.87$ (m, 1H, ArCOCH), 3.99 (td, J=7.0, $2.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}$ ), 3.84 (td, J=7.1, $2.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}$ ), 3.58 (ddd, $J=10.5,7.2,2.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}$ ), 3.46 (td, $J=11.5,3.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCH}$ ), 3.35 (td, $J=7.5,3.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}$ ), $3.10-2.98(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArCHCH}), 2.66-2.47(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArCHCH}), 2.43$ - $2.23\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{COCHCH}_{2}\right), 2.15-1.99\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{COCHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ б 201.6, 139.4, 138.1, 132.5, 128.4, 128.2, 128.1, 128.0, 126.6, 68.4, 67.3, 57.2, 57.0, 52.3, 48.6, 27.9. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2937 (w), 2856 (w), 1676 (s), 1599 (m), 1452 (m), 1361 (m), 1222 (s). HRMS (ESI/QTOF) m/z: [M + $\mathrm{Na}^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{20} \mathrm{NaO}_{2}{ }^{+}$315.1356; Found 315.1356.

7b2 $\left(3.50 \mathrm{mg}, 12.0 \mu \mathrm{~mol}, 12 \%\right.$ yield). TLC: $\mathrm{R}_{\mathrm{f}}=0.19\left(\mathrm{SiO}_{2}, 3: 1\right.$ pentane:Et $\left.{ }_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\mathrm{CDCl}_{3}$ ) $\delta 7.86-7.75(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.56-7.47(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.43-7.33$ (m, 2H, ArH), $7.29-7.23$ (m, 2H, ArH), $7.23-7.16(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH}), 4.39$ (ddd, $J=11.0,7.8,3.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{PhCH}), 3.90(\mathrm{t}, J=7.0 \mathrm{~Hz}, 2 \mathrm{H}$, $\mathrm{OCH}_{2}$ ), 3.73 (dd, $J=11.6,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), $3.55-3.41\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{OCH}_{2}\right), 2.85-2.70(\mathrm{~m}, 1 \mathrm{H}$, ArCHCH), $2.70-2.57(\mathrm{~m}, 1 \mathrm{H}, \operatorname{ArCHCHCH}), 2.10\left(\mathrm{q}, J=11.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}_{2}\right), 2.05-1.96(\mathrm{~m}, 1 \mathrm{H}$, $\mathrm{ArCOCH} 2) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) б 200.5, 142.9, 136.2, 133.3, 128.84, 128.79, 128.70, 127.2, 126.8, 68.0, 67.7, 61.8, 59.2, 52.2, 45.9, 29.8. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2939 (m), 2864 (w), 1679 (s), 1598 (w), 1496 (w), 1450 (m), 1350 (w), 1224 (m), 986 (m). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{20} \mathrm{NaO}_{2}{ }^{+} 315.1356$; Found 315.1352.

7b3 ( $5.9 \mathrm{mg}, 20 \mu \mathrm{~mol}, 20 \%$ yield). TLC: $\mathrm{R}_{\mathrm{f}}=0.22\left(\mathrm{SiO}_{2}, 3: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) б $7.80-7.74$ (m, 2H, ArH), $7.47-7.41$ (m, 1H, ArH), 7.32 (dd, $J=8.5,7.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $7.26-7.17$ (m, 4H, ArH), $7.13-7.07(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 4.01-3.90(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArCOCH}), 3.84(\mathrm{dd}, J=9.1,1.8 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{OCH}_{2}$ ), 3.75 (dd, $J=9.0,2.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}$ ), 3.62 (dd, $J=9.0,6.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}$ ), 3.53 (dd, $J=9.2$, $6.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{OCH}_{2}$ ), 3.37 (dd, $\mathrm{J}=11.0,9.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCH}$ ), $3.04-2.91\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}\right), 2.91-2.82(\mathrm{~m}$, $1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}$ ), $\left.2.53-2.41(\mathrm{~m}, 1 \mathrm{H}, \operatorname{ArCOCHCH})_{2}\right), 1.72\left(\mathrm{td}, \mathrm{J}=12.3,8.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCHCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 200.3,142.4,137.2,133.0,128.7,128.6,128.3,127.9,126.8,74.5,73.1,56.6$, 55.0, 53.4, 44.1, 39.0. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2959 (m), 2853 (m), 1677 ( s$), 1598$ (w), 1494 (w), 1450 (m), 1240
(m), 1020 (m), $980(\mathrm{~m}), 913(\mathrm{~m})$. HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{20} \mathrm{NaO}_{2}{ }^{+}$315.1356; Found 315.1362.

7b4 ( $7.3 \mathrm{mg}, 25 \mu \mathrm{~mol}, 25 \%$ yield). TLC: $\mathrm{R}_{\mathrm{f}}=0.26\left(\mathrm{SiO}_{2}, 3: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) б $7.72-7.66(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.49-7.39(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.33(\mathrm{dd}, \mathrm{J}=8.4,7.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $7.11-7.02$ (m, 3H, ArH), $6.95-6.90(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 4.29(\mathrm{q}, \mathrm{J}=6.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOH}), 3.89-3.74\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{OCH}_{2}\right)$, $3.73-3.68\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{OCH}_{2}\right), 3.40(\mathrm{dd}, J=7.1,5.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCH}), 3.25-3.12(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArCHCHCH}), 2.52$ (ddd, $J=13.3,8.4,6.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 1.77 (ddd, $J=13.2,6.7,4.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( 101 MHz , $\left.\mathrm{CDCl}_{3}\right)$ б 201.3, 140.6, 137.8, 132.8, 128.5, 128.3, 128.3, 128.2, 126.8, 75.9, 74.8, 56.1, 52.8, 51.1, 43.7, 35.4. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2959 (m), 2849 (m), 1679 (s), 1598 (w), 1450 (m), 1215 (m), 1077 (m), 915 (m). HRMS (ESI/QTOF) m/z: $[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{20} \mathrm{NaO}_{2}{ }^{+} 315.1356$; Found 315.1359.

## (2,3,4,5-Tetrahydro-[1,1'-biphenyl]-2,5-diyl)bis(phenylmethanone) (9a)



Following general procedure F, starting from $8(26.4 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 a}$ ( 51.0 mg , 0.50 mmol , 5 equiv.) in 1 mL CH 3 OH the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 100:0 to $90: 10$ ) affording 9 b ( $20.9 \mathrm{mg}, 57.1 \mu \mathrm{~mol}, 57 \%$ yield for both diastereomers) as a sticky oil mixture of two diastereomers. The $\mathrm{dr}(61: 39)$ was determined by integrating the NMR signals of ArCCH 6.30 ppm (major), 6.34 ppm (minor).

TLC: $\mathrm{R}_{\mathrm{f}}=0.28\left(\mathrm{SiO}_{2}, 5: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ):

## Aromatic:

$\delta 8.10-8.04$ ( $\mathrm{m}, 2 \mathrm{H}$ minor ), $7.99-7.95$ ( $\mathrm{m}, 4 \mathrm{H}$ for major and 2 H for minor) $7.56-7.50(\mathrm{~m}, 2 \mathrm{H}$ ) overlapped for both diastereomer, $7.49-7.40(\mathrm{~m}, 4 \mathrm{H})$ overlapped for both diastereomer, $7.23-7.19$ $(\mathrm{m}, 2 \mathrm{H})$. overlapped for both diastereomer, $7.17-7.08(\mathrm{~m}, 3 \mathrm{H})$. overlapped for both diastereomer.

Alkenyl and aliphatic :
Major: $\delta 6.30$ (d, J=3.9 Hz, 1H, ArCCH), 4.79-4.73 (m, 1H, ArCOCH), 4.39-4.31 (m, 1H, ArCOCH), $2.41-2.30\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.09-1.86\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{CH}_{2}\right)$ overlapped for both diastereomers.

Minor: $\delta 6.34$ ( $\mathrm{d}, \mathrm{J}=3.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCCH}$ ), $4.70-4.67$ ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), $4.16-4.08$ ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 2.25-2.17 (m, 2H, CH2), 2.09-1.86 (m, 2H, CH ${ }_{2}$ ) overlapped for both diastereomers.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) for both diastereomers ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 200.72,200.71,200.6,200.2$, $141.3,141.2,138.8,137.8,136.20,136.18,136.09,135.98,133.4,133.3,133.2,133.1,129.04,128.97$, $128.95,128.85,128.8,128.71,128.66,128.60,128.53,128.49,127.43,127.40,126.4,126.0,125.92$, 125.88, 46.3, 45.4, 45.3, 43.5, 26.2, 25.4, 22.0, 21.7.

IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 3061 (w), 2938 (w), 2251 (w), 1679 ( s$), 1596$ (m), 1447 (m), 1210 (s), 913 (m) HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{26} \mathrm{H}_{22} \mathrm{NaO}_{2}{ }^{+}$389.1512; Found 389.1521.
(4'-Methoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2,5-diyl)bis(phenylmethanone) (9b)


Following general procedure E, starting from 8 ( $26.4 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and 3 c ( 66.0 mg , $0.250 \mathrm{mmol}, 5.0$ equiv.) and $1 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{OH}$ the reaction mixture was stirred for 48 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 100:0 to $90: 10$ ) affording $9 \mathbf{b}(23.4 \mathrm{mg}, 59.1 \mu \mathrm{~mol}, 51 \%$ yield for both diastereomers) as a colorless oil as a mixture of two diastereomers. The $\mathrm{dr}(68: 32)$ was determined by integrating the NMR signals of ArCOCH 4.22 ppm (major), 4.02 ppm (minor).

TLC: $\mathrm{R}_{\mathrm{f}}=0.25\left(\mathrm{SiO}_{2}, 4: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

## Aromatic

$\delta 8.15-8.08(\mathrm{~m}, 2 \mathrm{H})$ minor, $8.05-8.00(\mathrm{~m}, 4 \mathrm{H}$ for major and 2H for minor), $7.23-7.16(\mathrm{~m}, 2 \mathrm{H})$ overlapped for both diastereomers. 6.76-6.69 (m,2H) overlapped for both diastereomers

## Alkenyl and aliphatic

Major diastereomer: ठ 6.27 (d, $J=4.0 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArCCH}$ ), 4.77 (t, $J=5.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 4.44 - 4.36 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), $3.71\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.46-2.36\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right) 2.11-1.90\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{CH}_{2}\right)$.

Minor diastereomer: $\delta 6.31$ (d, $J=2.8 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArCCH}$ ), 4.70 (t, $J=5.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 4.19 - 4.13 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 3.72 (s, 3H, $\mathrm{OCH}_{3}$ ), 2.28 - 2.21 ( $\mathrm{m}, 2 \mathrm{H}, \mathrm{CH}_{2}, \mathrm{CH}_{2}$ ), $2.10-1.94$ (m, 2H, CH 2 ).
${ }^{13} \mathrm{C}$ NMR for both diastereomers ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 200.9,200.8,200.8,200.3,159.0,159.0,138.1$, 137.1, 136.2, 136.1, 136.0, 133.8, 133.7, 133.3, 133.3, 133.2, 133.1, 129.1, 129.0, 128.9, 128.8, 128.7, 128.7, 128.7, 127.0, 126.9, 124.9, 124.4, 113.9, 113.9, 55.3 (one signal overlapped), 46.4, 45.5, 45.3, 43.4, 26.2, 25.4, 22.0, 21.6.

IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 3061 (w), 2935 (w), 2837 (w), 1680 (s), 1606 (m), 1578 (m), 1512 (s), 1448 (m), 1289 (m), 1250 (s), 1210 (s), 1030 (m). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{27} \mathrm{H}_{24} \mathrm{NaO}_{3}{ }^{+}$419.1618; Found 419.1623.
(1S,2R)-4,4-dimethyl-2-phenylcyclopentan-1-ol (4da)


To a solution of $\mathbf{4 d}$ ( $69.2 \mathrm{mg}, 0.200 \mathrm{mmol}$, 1 equiv) in $\mathrm{MeOH}(0.05 \mathrm{M}$ ) was added $\mathrm{TfOH}(9.00 \mathrm{mg}, 60.0$ $\mu \mathrm{mol}, 0.3$ equiv) under $\mathrm{N}_{2}$ atmosphere. The solution was heated to reflux until full conversion as indicated by TLC. The resulted mixture was then quenched by sat. $\mathrm{NaHCO}_{3}(2 \mathrm{~mL})$, extracted with $\mathrm{Et}_{2} \mathrm{O}$ ( $3 \times 5 \mathrm{~mL}$ ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated over reduced pressure to obtain a crude mixture 4d containing only the trans isomer. The crude was then directly used for the next step without further purification,

Crude NMR: ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.89(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $7.64(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $7.28-7.20(\mathrm{~m}, 4 \mathrm{H}, \mathrm{ArH}) 7.20-7.10(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 3.99-3.87(\mathrm{~m}, 2 \mathrm{H}, \operatorname{ArCOCH}), 2.19-2.01(\mathrm{~m}, 2 \mathrm{H}$, $\mathrm{CH}_{2}$ ), $1.98-1.83\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}\right.$ ), 1.78 (ddd, $J=12.8,5.9,2.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $1.24\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.16(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{CH}_{3}$ ). consistent with reported value. ${ }^{1 \mathrm{~b}}$

Following a reported procedure, ${ }^{16}$ the crude mixture from the previous step was added to a small flamedried vial with a magnetic stirring bar and m-CPBA ( $<77 \%$ purity, $78.0 \mathrm{mg}, 450 \mu \mathrm{~mol}$ ), and DCM ( 3.0 mL ). The vial was capped with a septum and three-cycle of $\mathrm{N}_{2}$ - vacuum was performed, then cooled to $0^{\circ} \mathrm{C}$. Trifluoroacetic acid ( $36.4 \mu \mathrm{~L}, 200 \mu \mathrm{~mol}, 1.0$ equiv.) was then added slowly via syringe. The vial was then covered with an aluminum foil, and the reaction mixture was stirred for 48 h at room temperature. After that, aqueous $\mathrm{Na}_{2} \mathrm{SO}_{3}$ was added to quench the reaction and the mixture was extracted with DCM ( $2 \times 5 \mathrm{~mL}$ ). The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude mixture was analyzed by NMR to confirm the product.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.12$ (d, $J=8.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $7.69(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.35-7.26$ (m, 4H, ArH), $7.26-7.18\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}\right.$ ), 5.45 (td, $J=8.0,5.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCO}_{2} \mathrm{CH}$ ), 3.57 (dt, J=11.9, 7.9 $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{PhCH}$ ), $2.29\left(\mathrm{dd}, J=13.7,8.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.13-1.96\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.78-1.67(\mathrm{~m}, 2 \mathrm{H}$, $\left.\mathrm{CH}_{2}\right), 1.26\left(\mathrm{~d}, \mathrm{~J}=4.4 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.20\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right)$. HRMS (APPI/LTQ-Orbitrap) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{21} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{NaO}_{2}{ }^{+}$385.1386; Found 385.1392 . data matching with literature. ${ }^{1 \mathrm{~b}}$

The crude mixture from the previous step was then added to a flame-dried vial with $\mathrm{MeOH}(2 \mathrm{~mL})$. A solution of sat. LiOH was added ( 1 mL ). The solution was stirred at room temperature overnight. After that, the solution was evaporated under reduced pressure then extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 5 \mathrm{~mL})$, concentrated under reduced pressure and isolated by Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 90:10 to $70: 30$ ) affording 4da ( $20.8 \mathrm{mg}, 109 \mu \mathrm{~mol}, 55 \%$ yield for 3 steps) as a colorless oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.27\left(\mathrm{SiO}_{2}, 4: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.39-7.26(\mathrm{~m}, 4 \mathrm{H}, \mathrm{ArH}), 7.26$ $-7.19(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 4.23(\mathrm{q}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHOH}), 3.05(\mathrm{dt}, J=12.0,8.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{PhCH}), 2.02$ (dd, $J$ $\left.=12.9,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.97-1.91\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.70-1.60\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.19\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.13$ $\left(\mathrm{s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right)$. Product formed a strong hydrogen bonding with $\mathrm{H}_{2} \mathrm{O}$ with overlapped signal at 1.6 ppm . ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 142.8,128.7,127.6,126.7,79.8,54.1,49.2,47.3,35.4,31.8,31.6$. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 3374 (w - broad), 2952 (s), 2865 (m), 1461 (m), 1325 (s), 1169 (m), 1133 (s), 1067 (s). HRMS (APPI/LTQ-Orbitrap) m/z: [M + H-1] ${ }^{+}$Calcd for $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{O}^{+}$189.1274; Found 189.1276.

## Unsuccessful alkynes and alkenes


n.r.

n.r.

n.r.


n.r.

n.r.

n.r.


20\% NMR yield after 48 hours

Unsuccessful other small ring.


n.r.

## Synthesis of $[2 \sigma+2 \sigma]$ products. <br> Trimethyl 4-benzoyl-5-phenylbicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10a)



Following general procedure F, starting from 1b ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and 11a ( 47 mg , 0.25 mmol , 2.5 equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to $60: 40$ ) affording $\mathbf{1 0 a}(32.4 \mathrm{mg}, 0.0720 \mathrm{mmol}, 72 \%)$ as sticky oil.

TLC: $\mathrm{R}_{\mathrm{f}}=0.4\left(\mathrm{SiO}_{2}, 70: 30\right.$ pentane:EtOAc) ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.57-7.51(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.41-$ $7.34(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.25-7.19(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.10-7.04(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 6.96(\mathrm{tt}, J=7.9,1.3 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{ArH})$, $4.18(\mathrm{t}, \mathrm{J}=8.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 3.84\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.70\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.25(\mathrm{dd}$, $J=10.6,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}$ ) , 2.95-2.87 (m, 2H, CHCH 2$), 2.80\left(\mathrm{~d}, J=10.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.56(\mathrm{dd}, J=$ $10.6,1.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $2.17\left(\mathrm{dd}, J=10.5,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 202.3$, 172.6, 172.3, 171.8, 145.1, 137.5, 132.8, 128.2, 128.2, 128.1, 126.4, 125.8, 59.2, 53.2, 53.0, 52.5, 49.0, 48.3, 45.7, 42.5, 34.6, 30.9. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2953 (w), 1730 ( s$), 1677$ (m), 1598 (w), 1447 (m), 1436 (m), 1264 (s), 1216 (s), 1109 (m), 913 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{26} \mathrm{H}_{26} \mathrm{NaO}_{7}^{+}$473.1571; Found 473.1580.

## Trimethyl 4-(4-bromobenzoyl)-5-phenylbicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10b)



Following general procedure $F$, starting from 1q ( $34.1 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and 11a ( 47.0 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to $60: 40$ ) affording $\mathbf{1 0 b}(32.3 \mathrm{mg}, 0.0612 \mathrm{mmol}, 61 \%)$ as white solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.23\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). Mp: $146-150{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.41-7.31$ (m, 4H, ArH), 7.13-7.03 (m, 2H, ArH), 7.02-6.95 (m, 1H, ArH), 6.95-6.88 (m, 2H, ArH), 4.12-4.07 (m, $1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.83\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.70\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.22(\mathrm{dd}, J=10.6,7.8 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.99-2.82 (m, 2H, CHCH2), $2.79\left(\mathrm{~d}, \mathrm{~J}=10.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.56-2.50\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.17$ (dd, $J=10.6,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.4,172.5,172.2,171.8,144.9$, 136.2, 131.5, 129.6, 128.3, 128.0, 126.6, 125.7, 59.1, 53.2, 53.0, 52.5, 49.1, 48.3, 45.8, 42.3, 34.6, 30.7. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2953 (w), 1734 ( s$), 1678$ (m), 1585 (m), 1435 (m), 1268 (s), 1216 (s), 1111 (m), 914 (w). HRMS (ESI/QTOF) m/z: [M+H] ${ }^{+}$Calcd for $\mathrm{C}_{26} \mathrm{H}_{26} \mathrm{BrO}_{7}{ }^{+}$529.0856; Found 529.0867.

## Trimethyl 4-(4-fluorobenzoyl)-5-phenylbicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10c)



Following general procedure $F$, starting from $1 \mathbf{r}(28.0 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and 11 a ( 47.0 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture
was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from $85: 15$ to $60: 40$ ) affording 11c ( $32.8 \mathrm{mg}, 0.0700 \mathrm{mmol}, 70 \%$ ) as white solid.

TLC: $\mathrm{R}_{\mathrm{f}}=0.32\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). Mp: 137-139 ${ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $\left.400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.59-7.51$ (m, 2H, ArH), 7.11-7.02 (m, 2H, ArH), 7.00-6.94 (m, 1H, ArH), 6.94-6.83 (m, 4H, ArH), 4.16-4.07 (m, $1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.83\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.70\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right) 3.23(\mathrm{dd}, J=10.6,7.8 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $2.94\left(\mathrm{dd}, J=14.5,8.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right.$ ), $2.86\left(\mathrm{dd}, J=14.5,7.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.80(\mathrm{~d}, J$ $=10.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $2.54\left(\mathrm{~d}, J=10.6,1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.18\left(\mathrm{dd}, J=10.5,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 200.7,172.5,172.3,171.8,166.8,164.2,145.0,133.9(\mathrm{~d}, \mathrm{~J}=3.0 \mathrm{~Hz}), 130.8(\mathrm{~d}, \mathrm{~J}$ $=9.2 \mathrm{~Hz}), 127.0(\mathrm{~d}, J=248.9 \mathrm{~Hz}), 126.5,115.3(\mathrm{~d}, J=22.0 \mathrm{~Hz}), 59.2,53.2,53.0,52.5,49.0,48.3,45.8$, 42.4, 34.6, 30.7. ${ }^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-105.5--105.7(\mathrm{~m})$. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) $2953(\mathrm{w}), 1732(\mathrm{~s})$, 1678 (m), 1597 (m), 1436 (m), 1266 ( s$), 1218$ ( s$), 1109$ (m), 914 (m), 734 (m). HRMS (ESI/QTOF) m/z: $[\mathrm{M}+\mathrm{H}]^{+}$Calcd for $\mathrm{C}_{26} \mathrm{H}_{26} \mathrm{FO}_{7}^{+}$469.1657; Found 469.1662.
Trimethyl 4-(4-methoxybenzoyl)-5-phenylbicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10d)


Following general procedure $F$, starting from $1 \mathrm{~s}(29.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.00$ equiv.) and 11a ( 47.0 $\mathrm{mg}, 0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from $85: 15$ to $60: 40$ ) affording 10d ( $25.4 \mathrm{mg}, 0.0529 \mathrm{mmol}, 53 \%$ ) as off-white amorphous solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.27\left(\mathrm{SiO}_{2}, 70: 30\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.59-7.52(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.12-7.04(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 6.97(\mathrm{tt}, J=8.1,1.3 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{ArH}), 6.73-6.66(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 4.12(\mathrm{t}, \mathrm{J}=8.2 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 3.83\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.81\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.77\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.70\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.26$ (dd, $J=10.6,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $2.88\left(\mathrm{dd}, J=8.3,6.8 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.79(\mathrm{~d}, J=10.5 \mathrm{~Hz}, 1 \mathrm{H}$, $\left.\mathrm{CCH}_{2}\right), 2.58-2.52\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.15\left(\mathrm{dd}, J=10.5,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ $200.5,172.6,172.4,171.8,163.3,145.3,130.5,130.5,128.1,126.3,125.8,113.4,59.3,55.5,53.1$, $53.0,52.5,48.5,48.3,45.6,42.5,34.7,31.0$. IR $\left(\mathrm{v}_{\max }, \mathrm{cm}^{-1}\right) 2952(\mathrm{w}), 2842(\mathrm{w}), 1729(\mathrm{~s}), 1668(\mathrm{~m})$, 1602 (s), 1433 (m), 1258 (s), 1218 (s), 1172 (s). HRMS (ESI/QTOF) m/z: [M+H]+ Calcd for $\mathrm{C}_{27} \mathrm{H}_{29} \mathrm{O}_{8}{ }^{+}$481.1857; Found 481.1861.

## 2-(Tert-butyl) 1-methyl 4-benzoyl-5-phenylbicyclo[3.1.1]heptane-1,2-dicarboxylate (10e)



Following general procedure F, starting from $\mathbf{1 i}(24.6 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 a}(47.0 \mathrm{mg}$, $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3} \mathrm{CN}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from $85: 15$ to $60: 40$ ) affording $\mathbf{1 0 e}(18.3 \mathrm{mg}, 0.0422 \mathrm{mmol}, 42 \%)$ as off-white amorphous solid. The product was isolated as a mixture of 2 diastereoisomers. The diastereomeric ratio (76:24) was determined by integrations of the NMR signals of ArCOCH in the 4.15 ppm (major), 4.23 ppm (minor) crude mixture. The NMR data is reported for the major diastereoisomer.
TLC: $\mathrm{R}_{\mathrm{f}}=0.40\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc $) .{ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.59-7.51(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7.42-7.35 (m, 1H, ArH), 7.25-7.20 (m, 2H, ArH), 7.12-7.04 (m, 2H, ArH), 7.01-6.93 (m, 3H, ArH), 4.15 (t, $J=8.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 3.68 (s, 3H, OCH3), 3.26 (ddd, $J=9.4,8.2,1.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCO}_{2} \mathrm{tBu}$ ), 2.95 (dd, $J=10.5,7.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.70 (dt, $J=10.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.53-2.35 (m, 3H, CHCH2CH
and $\mathrm{CCH}_{2}$ ), 2.19-2.11 (m, 1H, CCH 2 ), $1.44\left(\mathrm{~s}, 9 \mathrm{H}, \mathrm{C}\left(\mathrm{CH}_{3}\right)_{3}\right) .{ }^{13} \mathrm{C} \operatorname{NMR}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 202.6,174.3$, 173.2, 145.6, 137.7, 132.7, 128.3, 128.1, 128.1, 126.2, 126.0, 81.1, 51.9, 50.0, 46.4, 46.3, 45.9, 44.8, 30.2, 28.1, 26.6. IR ( $\mathrm{v}_{\max }, \mathrm{cm}^{-1}$ ) 2936 (w), 1728 ( s$), 1677$ (m), 1451 (m), 1367 (m), 1283 (m), 1219 (s), 1158 (s), 1109 (m), 911 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{27} \mathrm{H}_{30} \mathrm{NaO}_{5}{ }^{+} 457.1985$; Found 457.1987.

Trimethyl 4-benzoyl-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10f)


Following general procedure F, starting from $\mathbf{1 b}$ ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 b}$ ( 51.5 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to 60:40) affording $10 f(39.3 \mathrm{mg}, 0.0839 \mathrm{mmol}, 84 \%)$ as white solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.25\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). Mp: $141-143{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.67-7.58$ (m, 2H, ArH), 7.44-7.36 (m, 1H, ArH), 7.25 (s, 2H, ArH), 6.98-6.92 (m, 1H, ArH), 6.92-6.86 (m, 2H, ArH ), 6.69-6.63 (m, 1H, ArH), 4.40 (t, J=8.3 Hz, 1H, C(O)CH), 3.84 (s, 3H, OCH3), $3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), $3.71\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.28\left(\mathrm{dd}, \mathrm{J}=10.5,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.95-2.82\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{CHCH}_{2}\right.$ and $\left.\mathrm{CCH}_{2}\right), 2.54$ (d, $J=10.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}$ ), 2.25 (ddd, $J=11.0,7.8,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}$ ).$^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 201.9, 172.4, 172.2, 171.4, 160.4 (d, $J=245.3 \mathrm{~Hz}$ ), 137.1, 132.9, $131.2(\mathrm{~d}, J=14.8 \mathrm{~Hz}), 129.81(\mathrm{~d}, J$ $=8.6 \mathrm{~Hz}), 128.8(\mathrm{~d}, J=5.3 \mathrm{~Hz}), 128.4(\mathrm{~d}, J=8.2 \mathrm{~Hz}), 128.2,127.9,115.1(\mathrm{~d}, J=21.4 \mathrm{~Hz}), 59.0,53.1$, $52.9,52.4,48.7,46.6,43.4,42.8(\mathrm{~d}, J=3.0 \mathrm{~Hz}), 34.7,30.4 .{ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-115.95$ (ddt, $J=11.6,8.7,4.8 \mathrm{~Hz})$. IR $\left(\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}\right) 2954(\mathrm{w}), 1732(\mathrm{~s}), 1678(\mathrm{~m}), 1492(\mathrm{~m}), 1450(\mathrm{~m}), 1436(\mathrm{~m}), 1263$ (s), 1222 (s), 1120 (m), 914 (w), 760 (m), 734 (m). HRMS (ESI/QTOF) m/z: [M+Na]+ Calcd for $\mathrm{C}_{26} \mathrm{H}_{25} \mathrm{FNaO}_{7}^{+}$491.1477; Found 491.1482.

## Trimethyl 4-([1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate $(10 \mathrm{~g})$



Following general procedure F, starting from 1 t ( $33.8 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 b}$ ( 51.5 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to $60: 40$ ) affording product $\mathbf{1 0 g}(40.3 \mathrm{mg}, 0.0740 \mathrm{mmol}, 74 \%)$ as white solid.

TLC: $\mathrm{R}_{\mathrm{f}}=0.21\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). Mp: $148-151^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.73-7.68$ (m, 2H, ArH), 7.57-7.51 (m, 2H, ArH), 7.50-7.45 (m, 2H, ArH), 7.45-7.40 (m, 2H, ArH), 7.40-7.35 (m,

1H, ArH), 6.98-6.93 (m, 1H, ArH), 6.93-6.88 (m, 2H, ArH), 6.73-6.64 (m, 1H, ArH), $4.43(\mathrm{t}, \mathrm{J}=8.3 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.85\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.83\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.72\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.29(\mathrm{dd}, \mathrm{J}=10.6,7.9 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.94 (dd, $J=8.3,5.9 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CHCH}_{2}$ ), 2.88 (d, $J=11.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}$ ), 2.56 (d, $J=10.8$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.27 (ddd, $J=11.0,7.8,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.6,172.5$, $172.4,171.6,161.8,159.3145 .6,139.9,135.9,131.4(\mathrm{~d}, J=14.7 \mathrm{~Hz}) 129.1,128.8(\mathrm{~d}, J=35.3 \mathrm{~Hz})$, 128.5, 128.3, $128.2(\mathrm{~d}, J=174.1 \mathrm{~Hz}), 127.8(\mathrm{~d}, J=174.0 \mathrm{~Hz}) 123.9(\mathrm{~d}, J=3.0 \mathrm{~Hz}), 115.3(\mathrm{~d}, J=21.3$ $\mathrm{Hz}) 59.2,53.2,53.0,52.5,48.9,46.8,43.6,43.0,34.9,30.6 .{ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-115.9(\mathrm{dd}$, $J=7.3,3.6 \mathrm{~Hz}$ ). IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2953 (w), 1734 (s), 1675 (m), 1603 (w), 1491 (w), 1451 (m), 1264 (s), 1224 (s), 1121 (m), 757 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{32} \mathrm{H}_{29} \mathrm{FNaO}_{7}^{+}$567.1790; Found 567.1790.

Trimethyl 4-(dibenzo[b,d]furan-2-carbonyl)-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate (10h)


Following general procedure $F$, starting from $\mathbf{1 u}(35.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 b}$ ( 51.5 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from $85: 15$ to $60: 40$ ) affording product $\mathbf{1 0 h}(13.4 \mathrm{mg}, 0.0240 \mathrm{mmol}, 24 \%)$ as off-white amorphous solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.18\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.26(\mathrm{~d}, J=1.8 \mathrm{~Hz}, 1 \mathrm{H}$, ArH), 7.95 (ddt, $J=9.1,7.6,1.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), $7.82-7.77$ ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.56 (ddt, $J=8.0,6.9,0.9 \mathrm{~Hz}$, 1H, ArH), 7.53-7.46 (m, 2H, ArH), 7.41-7.33 (m, 1H, ArH), 6.92-6.83 (m, 3H, ArH), 6.61 (dtd, J=7.7, $6.2,2.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 4.57-4.48 (m, 1H, C(O)CH), $3.87\left(\mathrm{~d}, \mathrm{~J}=1.6 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.84\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $3.72\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.33$ (dd, $J=10.5,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 3.04 (dd, J=14.4, $9.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}$ ), 2.99$2.93\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.93-.88\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.57\left(\mathrm{~d}, \mathrm{~J}=10.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.32$ (ddt, $J=11.0$, $9.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.0,172.5,172.4,171.7,157.9$ (d, J=199.5 $\mathrm{Hz}) 136.2,132.6,128.9,128.6(\mathrm{~d}, J=8.2 \mathrm{~Hz}), 128.0(\mathrm{~d}, J=18.5 \mathrm{~Hz}), 124.3,124.0(\mathrm{~d}, J=3.2 \mathrm{~Hz})$, 123.8, 123.5 123.3, $123.0121 .6,121.5,121.1,120.2115 .2(\mathrm{~d}, J=21.3 \mathrm{~Hz}), 111.7$ (d, $J=57.9 \mathrm{~Hz})$, 59.2, 53.2, 53.0, 52.5, 48.9, 46.8, 43.8, 34.9, 30.6, 30.5. ${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-115.9$. IR ( $\mathrm{v}_{\text {max }}$, $\mathrm{cm}^{-1}$ ) 2953 (w), 1733 (s), 1676 (m), 1583 (w), 1491 (m), 1434 (m), 1252 (s), 1197 (s), 1120 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{32} \mathrm{H}_{27} \mathrm{FNaO}_{8}{ }^{+}$581.1582; Found 581.1590.

Dimethyl 4-benzoyl-2-chloro-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2-dicarboxylate (10i)


Following general procedure $F$, starting from $\mathbf{1 v}(23.8 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 b}$ ( 51.5 mg , 0.250 mmol , 2.5 equiv.) and $1 \mathrm{mLCH} \mathrm{CH}_{3} \mathrm{CN}$ in 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 15:85 to 60:40) to give mixture of the desired product along with another unidentified by-product. The mixture was then heated with $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ ( $65.2 \mathrm{mg}, 0.200 \mathrm{mmol}, 2.00$ equiv.) in $\mathrm{CH}_{3} \mathrm{CN}$ at $70{ }^{\circ} \mathrm{C}$ for 2 hours and purified by chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from $15: 85$ to $25: 75$ ) affording product $\mathbf{1 0 i}$ ( $18.7 \mathrm{mg}, 0.0421 \mathrm{mmol}, 42 \%$ mixture of two diastereoisomers) as off-white amorphous solid. The diastereomeric ratio was determined by integrating the NMR signals of ArCOCH 4.65 ppm (major), 4.49 ppm (minor) in the crude mixture (dr: 91:9). The NMR data is reported for the major diastereoisomer.
TLC: $\mathrm{R}_{\mathrm{f}}=0.41\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H} \operatorname{NMR}\left(800 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.65-7.59(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.40(\mathrm{tt}, J=7.3,1.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.26 (t, $J=7.2 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 6.96-6.88$ (m, 3H, ArH), 6.62 (ddd, $J=$ $11.0,7.8,1.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 4.65 (dd, $J=10.6,6.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 3.85 (s, 3H, OCH3), 3.70 (s, 3H, $\left.\mathrm{OCH}_{3}\right), 3.26-3.18\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArCHCH}_{2}\right), 3.01\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.79\left(\mathrm{~d}, \mathrm{~J}=10.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.70(\mathrm{~d}, \mathrm{~J}$ $\left.=10.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.48\left(\mathrm{dd}, \mathrm{J}=15.4,6.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right) .{ }^{13} \mathrm{C} \operatorname{NMR}\left(201 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 201.6$, $171.6,171.4,137.1,160.5(\mathrm{~d}, J=245.7 \mathrm{~Hz}), 133.2,130.7(\mathrm{~d}, J=14.9 \mathrm{~Hz}), 128.81(\mathrm{~d}, J=6.7 \mathrm{~Hz}), 128.76$ (d, $J=8.1 \mathrm{~Hz}), 128.4,128.0,124.0(\mathrm{~d}, J=3.3 \mathrm{~Hz}), 115.2(\mathrm{~d}, J=21.2 \mathrm{~Hz}), 72.5,53.7,53.0,52.5,45.5$, 44.7, 44.7, 44.7, 39.0, 34.7, 30.5. ${ }^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-115.5(\mathrm{~d}, J=6.8 \mathrm{~Hz}) . \operatorname{IR}\left(\mathrm{v}_{\max }, \mathrm{cm}^{-1}\right)$ 2953 ( w ), 1735 ( s$), 1678$ ( m ), 1492 (m), 1450 (m), 1317 (m), 1260 (s), 1223 (s), 1121 (m), 914 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{22} \mathrm{CIFNaO}_{5}{ }^{+} 467.1032$; Found 467.1036.

## Dimethyl 4-benzoyl-2-fluoro-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2-dicarboxylate (10j)



Following general procedure F, starting from $\mathbf{1 w}(22.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and 11b ( 51.5 $\mathrm{mg}, 0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3} \mathrm{CN}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from $85: 15$ to $60: 40$ ) affording product $\mathbf{1 0 j}$ ( $21.8 \mathrm{mg}, 0.0509 \mathrm{mmol}, 51 \%$ mixture of two diastereoisomers) as sticky oil. The diastereomeric ratio (dr $81: 19$ ) was determined by integration of the NMR signals of ArCOCH 4.66 ppm (major), 4.48 ppm (minor) in the crude mixture. The NMR data is reported for the major diastereomer.
TLC: $\mathrm{R}_{\mathrm{f}}=0.44\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc).
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ) ס 7.65-7.60 (m, 2H, ArH), 7.43-7.38 (m, 1H, ArH), 7.27 (d, J=7.6 Hz, 2H, ArH), 6.97-6.89 (m, 3H, ArH), 6.66-6.60 (m, 1H, ArH), 4.66 (dd, J=10.1, 7.0 Hz, 1H, C(O)CH), 3.86 $\left(\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.72\left(\mathrm{~d}, \mathrm{~J}=1.6 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.15\left(\mathrm{ddd}, J=10.5,7.8,2.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 3.08-2.99$ ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $2.87\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.79\left(\mathrm{dd}, J=10.8,4.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.65(\mathrm{dd}, J=10.4,2.5 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.44-2.32 (m, 1H, CHCH2).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 201.6, 171.5, 171.2, 160.4 (d, $J=245.3 \mathrm{~Hz}$ ), 137.0, 130.6 (d, J=14.9 $\mathrm{Hz}), 130.0,128.6(\mathrm{~d}, J=12.1 \mathrm{~Hz}), 128.0(\mathrm{~d}, J=33.9 \mathrm{~Hz}), 123.9(\mathrm{~d}, J=3.2 \mathrm{~Hz}), 115.1(\mathrm{~d}, J=21.3 \mathrm{~Hz})$, $96.1,52.8,52.4,50.5(\mathrm{~d}, J=21.5 \mathrm{~Hz}), 45.1,44.4,41.4(\mathrm{dd}, J=11.0,3.2 \mathrm{~Hz}), 34.3(\mathrm{~d}, J=5.1 \mathrm{~Hz}), 33.5$ (d, $J=24.2 \mathrm{~Hz}) .{ }^{19}$ F NMR ( $377 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-115.8(\mathrm{~d}, J=10.7 \mathrm{~Hz}$ ), -156.3 (dd, $J=37.2,20.6 \mathrm{~Hz}$ ). IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 3005 (w), 2955 (w), 1765 (m), 1735 (s), 1678 (m), 1596 (w), 1492 (m), 1449 (m), 1264 (s), 1225 (s), 1118 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{24} \mathrm{H}_{22} \mathrm{~F}_{2} \mathrm{NaO}_{5}{ }^{+} 451.1328$; Found 451.1336.

Dimethyl 4-benzoyl-5-(2-fluorophenyl)-2-(((13S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)bicyclo[3.1.1]heptane-1,2-dicarboxylate (10k)


Following general procedure F, starting from 1x ( $47.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 b}$ ( 51.5 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3} \mathrm{CN}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from $85: 15$ to $60: 40$ ) affording product $\mathbf{1 0 k}(14.2 \mathrm{mg}, 0.0209 \mathrm{mmol}, 21 \%$ mixture of two diastereoisomers) as offwhite amorphous solid. The diastereomeric ratio was determined by integrating the NMR signals of ArCOCH 4.38 ppm (major), 4.62 ppm (minor) in the crude mixture (dr. $>95: 5$ ). The NMR data is reported for the major diastereoisomer.
TLC: $\mathrm{R}_{\mathrm{f}}=0.31\left(\mathrm{SiO}_{2}, 70: 30\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $\left.400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.53-7.47(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.35(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArH}), 7.22-7.15(\mathrm{~m}, 3 \mathrm{H}, \operatorname{ArH}), 6.91(\mathrm{q}, \mathrm{J}=5.6 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{ArH}), 6.81-6.73(\mathrm{~m}, 2 \mathrm{H}$, ArH), 6.68-6.60 (m, 1H, ArH), $4.38(\mathrm{t}, \mathrm{J}=8.6 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArC}(\mathrm{O}) \mathrm{CH}), 3.78\left(\mathrm{~d}, J=4.5 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.68$ (s, 3H, OCH ${ }_{3}$ ), 3.25 (tq, $J=9.4,4.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{H}$-estrone), 3.09 (ddd, $J=11.8,7.6,4.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}$-estrone), 2.89 (dd, $J=8.5,3.8 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{PhCOCH}_{2}$ ), $2.64\left(\mathrm{~d}, J=10.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.53-2.46\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CCH}_{2}\right)$, 2.37 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{H}$-estrone), 2.26 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{H}$-estrone), 2.19-2.11 (m, 1H, H-estrone), 2.05-1.98 (m, 2H, Hestrone and $\mathrm{CCH}_{2}$ ), 1.98-1.92 (m, 1H, H-estrone), 1.67-1.56 (m,3H, H-estrone), 1.51-1.41 (m, 4H, H-estrone), 0.91 (d, $J=1.5 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 221.1,201.6,172.8$, 172.6, $160.5(\mathrm{~d}, J=243.6 \mathrm{~Hz}), 150.0137 .8(\mathrm{~d}, J=5.2 \mathrm{~Hz}), 137.1,133.9$, 132.8, $128.9(\mathrm{~d}, J=5.2 \mathrm{~Hz}), 128.4$ (d, $J=8.1 \mathrm{~Hz}$ ), 128.1, 127.9, 126.1 (d, $J=6.5 \mathrm{~Hz}$ ), 123.8, 119.5, 119.4, 116.2 (d, $J=26.3 \mathrm{~Hz}), 115.1$ (d, $J=21.3 \mathrm{~Hz}$ ), $84.0,52.8,52.7,52.2,52.0,50.5,48.0,45.6,44.1(\mathrm{~d}, J=3.0 \mathrm{~Hz}), 42.9,41.3,38.3$, $35.9,34.4,31.6,29.6(\mathrm{~d}, \mathrm{~J}=12.0 \mathrm{~Hz}), 26.5,25.8,21.6,13.9 .{ }^{19} \mathrm{~F} \mathbf{N M R}\left(376 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta-115.8$. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2951 (w), 2870 (w), 1737 (s), 1681 (w), 1493 (s), 1451 (m), 1258 (m), 1226 (s), 1194 (m), 956 (m), 759 (m), 734 (s). HRMS (Nanochip-based ESI/LTQ-Orbitrap) m/z: [M+H]+ Calcd for $\mathrm{C}_{42} \mathrm{H}_{44} \mathrm{FO}_{7}{ }^{+}$679.3066; Found 679.3063.

## Trimethyl 4-benzoyl-5-(4-chlorophenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10I)



Following general procedure $F$, starting from $\mathbf{1 b}$ ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 c}(55.6 \mathrm{mg}$, $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3} \mathrm{CN}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to $60: 40$ ) affording $101(45.0 \mathrm{mg}, 0.0929 \mathrm{mmol}, 93 \%$ ) white solid.

TLC: $\mathrm{R}_{\mathrm{f}}=0.38\left(\mathrm{SiO}_{2}, 70: 30\right.$ pentane:EtOAc). Mp: 167-168 ${ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.64-7.55$ (m, 2H, ArH), 7.45 (t, J=7.4 Hz, 1H, ArH), $7.30(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.10-7.03(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 6.97-$ 6.87 (m, 2H, ArH), 4.16 ( $\mathrm{q}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), 3.85 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}_{3}$ ), 3.83 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}_{3}$ ), 3.73 ( s , $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), 3.25 (dd, $J=10.6,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $2.99-2.85\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.77(\mathrm{~d}, \mathrm{~J}=10.5 \mathrm{~Hz}$, $\left.1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.55\left(\mathrm{~d}, J=10.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.16\left(\mathrm{dd}, J=10.5,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , $\left.\mathrm{CDCl}_{3}\right)$ ס 202.1, 172.4, 172.1, 171.6, 143.7, 137.3, 133.1, 132.2, 128.5, 128.3, 128.1, 127.3, 59.1, 53.2, $53.0,52.6,49.0,48.2,45.2,42.5,34.6,31.0$. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 3004 (w), 2953 (w), 2258 (w), 1732 (s), 1676 (m), 1494 (w), 1435 (m), 1262 (s), 1216 (s), 1114 (m), 1096 (m), 1015 (m), 913 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{26} \mathrm{H}_{25} \mathrm{ClNaO}_{7}{ }^{+}$507.1181; Found 507.1173.

## Trimethyl 4-benzoyl-5-(4-(trifluoromethyl)phenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10m)



Following general procedure F, starting from 1b ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and 11 d ( 64.0 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to $60: 40$ ) affording $10 \mathrm{~m}(28.5 \mathrm{mg}, 0.0550 \mathrm{mmol}, 55 \%)$ as white solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.21\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). Mp: $181-183{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.57-7.52$ (m, 2H, ArH), 7.43-7.38 (m, 1H, ArH), $7.33(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.26-7.22(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.07(\mathrm{~d}, \mathrm{~J}$ $=8.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 4.18(\mathrm{t}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 3.84\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.81\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.71(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), 3.25 (dd, $J=10.6,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $3.00-2.84\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CHCH}_{2}\right.$ ), 2.77 (d, $J=10.5$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $2.58\left(\mathrm{dd}, J=10.6,0.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.20\left(\mathrm{dd}, J=10.5,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.8,172.3,172.1,171.6,149.1,137.2,133.2,129.9,128.5,128.3$ (d, J=39.5 Hz ), 126.3, 125.4, 125.2 (d, $J=3.8 \mathrm{~Hz}$ ), 59.1, 53.2, 53.1, 52.6, 49.0, 48.2, 45.5, 42.4, 34.5, 30.9. ${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$-62.7. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2954 ( w ), 1732 ( s$), 1678$ (m), 1436 (m), 1326 (s), 1269 (s), 1217 (s), 1165 (s), 1118 (s), 1066 (m), 1017 (m), 914 (m). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{27} \mathrm{H}_{25} \mathrm{~F}_{3} \mathrm{NaO}_{7}{ }^{+} 541.1445$; Found 541.1445.

Trimethyl 4-benzoyl-5-(4-(methoxycarbonyl)phenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10n)


Following general procedure $F$, starting from $\mathbf{1 b}(26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 e}(61.5 \mathrm{mg}$, $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 80:20 to $60: 40$ ) affording $\mathbf{1 0 n}(35.6 \mathrm{mg}, 0.0701 \mathrm{mmol}, 70 \%)$ as colorless oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.23\left(\mathrm{SiO}_{2}, 70: 30\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.79-7.74(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.59-7.54(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.39(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), $7.23(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $7.05(\mathrm{~d}, J=8.3 \mathrm{~Hz}$, $2 \mathrm{H}, \mathrm{ArH}$ ), $4.20(\mathrm{dd}, \mathrm{J}=9.2,7.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 3.84\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.83\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.81(\mathrm{~s}, 3 \mathrm{H}$, $\mathrm{OCH}_{3}$ ), $3.71\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.27\left(\mathrm{dd}, J=10.6,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.91-2.89\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.78(\mathrm{~d}$,
$J=10.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $2.58\left(\mathrm{~d}, J=10.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.20-2.15\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR (101 $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.9,172.4,172.1,171.6,166.9,150.4,137.1,133.2,129.6,128.5,128.2,128.1$, 125.9, 59.1, 53.2, 53.1, 52.6, 52.1, 48.8, 48.2, 45.6, 42.6, 34.6, 31.1. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2953 (w), 1725 (s), 1674 (m), 1436 (m), 1281 (s), 1217 (s), 1112 (s), 1018 (m), 917 (m). HRMS (Nanochip-based ESI/LTQOrbitrap) m/z: $[\mathrm{M}+\mathrm{H}]^{+}$Calcd for $\mathrm{C}_{28} \mathrm{H}_{29} \mathrm{O}_{9}{ }^{+} 509.1806$; Found 509.1808.

## Trimethyl 4-benzoyl-5-(4-(trifluoromethoxy)phenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (100)



Following general procedure F, starting from 1b ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and 11 f ( 68.0 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to $60: 40$ ) affording $\mathbf{1 0 0}(32.2 \mathrm{mg}, 0.0604 \mathrm{mmol}, 60 \%)$ as white solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.23\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). Mp: $159-160{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.54-$ $7.49(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.41-7.36(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.25-7.20(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 6.97-6.87(\mathrm{~m}, 4 \mathrm{H}, \mathrm{ArH}), 4.15(\mathrm{t}, \mathrm{J}$ $=8.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}), 3.84\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.71\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.22(\mathrm{dd}, \mathrm{J}=10.6$, $7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 3.00-2.85 (m,2H, CHCH2), 2.76 (d, $J=10.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}$ ), 2.52 (dd, $J=10.6,1.0$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.23-2.14 (m, 1H, CCH2). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 202.1, 172.4, 172.2, 171.7, 147.6, 147.6, 143.9, 137.4, 133.0, 128.4, 128.0, 127.3, 120.8, 59.1, 53.2, 53.0, 52.6, 49.1, 48.2, 45.3, 42.3, 34.6, 30.7. ${ }^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$-58.04. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2953 (w), 1742 (s), 1724 (s), 1676 (m), 1436 (m), 1267 (s), 1254 ( s$), 1205$ ( s$), 1174$ ( s$), 1159$ ( s$), 1115$ (m), 915 (m). HRMS (ESI/QTOF) $\mathrm{m} / \mathrm{z}:[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{27} \mathrm{H}_{25} \mathrm{~F}_{3} \mathrm{NaO}_{8}{ }^{+}$557.1394; Found 557.1400.

## Trimethyl 4-benzoyl-5-(3-methoxyphenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10p)



Following general procedure $F$, starting from $\mathbf{1 b}(26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 g}$ ( 57.8 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and 1 mLCH CN . The reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 80:20 to $60: 40$ ) affording $\mathbf{1 0 p}(14.4 \mathrm{mg}, 0.0300 \mathrm{mmol}, 30 \%$ ) as colorless oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.30\left(\mathrm{SiO}_{2}, 70: 30\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.59-7.54(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, 7.38 (ddt, $J=7.8,6.9,1.2 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArH}), 7.26-7.21(\mathrm{~m}, 2 \mathrm{H}, \operatorname{ArH}), 6.99(\mathrm{t}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArH}), 6.54$ (ddd, $J=7.6,1.6,1.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.50 (ddd, $J=8.3,2.6,1.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.45 (dd, $J=2.5,1.6 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{ArH}$ ), 4.16 (t, J= $8.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.83\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.71\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $3.64\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.22\left(\mathrm{dd}, \mathrm{J}=10.6,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right.$ ), 2.97-2.84 (m, 2H, ArCHCH 2$), ~ 2.79(\mathrm{~d}, J=$ $10.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.55 (dd, $J=10.6,0.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $2.15\left(\mathrm{dd}, J=10.5,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}\right.$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 202.2,172.6,172.3,171.8,159.4,146.7,137.6,132.8,129.3,128.2,128.1$, 118.2, 112.0, 111.7, 59.2, 53.2, 53.0, 52.5, 49.0, 48.2, 45.8, 42.5, 34.6, 30.8, 29.9. HRMS (ESI/QTOF)
$\mathrm{m} / \mathrm{z}$ : $[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{27} \mathrm{H}_{28} \mathrm{NaO}_{8}{ }^{+}$503.1676; Found 503.1675. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) $2952(\mathrm{w}), 1739(\mathrm{~s})$, 1681 (w), 1599 (w), 1435 (m), 1265 (s), 1219 (m), 1109 (m), 917 (w).

Trimethyl 4-benzoyl-5-(m-tolyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10q)


Following general procedure F, starting from 1b ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 h}$ ( 50.5 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from 85:15 to $60: 40$ ) affording $\mathbf{1 0 q}(34.8 \mathrm{mg}, 0.0750 \mathrm{mmol}, 75 \%)$ as colorless oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.23\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H} \mathbf{N M R}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.53(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H}$, ArH), 7.39-7.31 (m, 1H, ArH), 7.22 (t, J=7.6 Hz, 2H, ArH), 6.97-6.90 (m, 1H, ArH), 6.80-6.69 (m, 3H, ArH), 4.15 ( $\mathrm{q}, J=7.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.83\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.70\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, 3.22 (dd, $J=10.6,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.91 (m, 2H, $\mathrm{ArCHCH}_{2}$ ), 2.78 (d, $J=10.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.54 (d, $J=$ $10.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.19-2.15(\mathrm{~m}, 1 \mathrm{H}), 2.13\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{ArCH}_{3}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 202.3,172.6,172.3$, $171.8,145.0,137.7,137.6,132.7,128.11,128.09$, 127.1, 126.6, 122.7, 59.2, 53.1, 53.0, 52.5, 49.0, 48.3, 45.7, 42.5, 34.5, 30.7, 21.3. One carbon is unresolved or overlapping. IR ( $\mathrm{v}_{\mathrm{max}}, \mathrm{cm}^{-1}$ ) $2952(\mathrm{w})$, 1734 (s), 1678 (m), 1606 (w), 1436 (m), 1268 (s), 1222 (s), 1109 (m), 914 (w). HRMS (ESI/QTOF) m/z: $[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{27} \mathrm{H}_{28} \mathrm{NaO}_{7}{ }^{+}$487.1727; Found 487.1720.

1-Allyl 2,2-dimethyl 4-benzoyl-5-(4-chlorophenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10r)


Following general procedure F, starting from $\mathbf{1 b}$ ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and 11 i ( 62.0 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 16 h . The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from $85: 15$ to $60: 40$ ) affording $\mathbf{1 0 r}(26.5 \mathrm{mg}, 0.0519 \mathrm{mmol}, 52 \%)$ as colorless oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.25\left(\mathrm{SiO}_{2}, 80: 20\right.$ pentane:EtOAc $)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.59-7.53$ (m, 2H, ArH), 7.46-7.37 (m, 1H, ArH), 7.28 (dd, J = 7.1, 1.2 Hz, 2H, ArH), 7.09-7.03 (m, 2H, ArH), 6.94-6.85 (m, 2H, ArH), 5.89 (ddt, J=17.2, 10.3, 5.8 Hz, 1H, $\mathrm{OCH}_{2} \mathrm{CHCH}_{2}$ ), 5.34-5.14 (m, 2H, OCH $\mathrm{CHCH}_{2}$ ), 4.69-4.54 (m, 2H, OCH2CHCH 2$), 4.18-4.12(\mathrm{~m}, 1 \mathrm{H}$, $\mathrm{C}(\mathrm{O}) \mathrm{CH}$ ), $3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.79\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.25\left(\mathrm{dd}, \mathrm{J}=10.6,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.97-2.81(\mathrm{~m}$, $2 \mathrm{H}, \mathrm{ArCHCH}_{2}$ ), 2.76 (d, $J=10.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $2.53\left(\mathrm{dd}, J=10.6,1.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right.$ ), 2.14 (dd, $J=$ $\left.10.5,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 202.1,172.1,171.6,143.7,137.3,133.1,132.2$, 132.0, 128.5, 128.3, 128.1, 127.3, 118.7, 66.1, 59.2, 53.2, 53.0, 49.0, 48.2, 45.1, 42.6, 34.7, 31.0. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2953 (w), 1733 (s), 1678 (w), 1596 (w), 1494 (w), 1449 (w), 1267 (s), 1217 (s), 1114 (m), 1096 (m), 1015 (w), 828 (w). HRMS (ESI/QTOF) m/z: [M+Na] ${ }^{+}$Calcd for $\mathrm{C}_{28} \mathrm{H}_{27} \mathrm{CINaO}_{7}^{+} 533.1338$; Found 533.1343.


Following general procedure F, starting from $\mathbf{1 b}$ ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{1 1 j}$ ( 66.0 mg , $0.250 \mathrm{mmol}, 2.5$ equiv.) and $1 \mathrm{mLCH} \mathrm{CN}_{3}$ the reaction mixture was stirred for 18 h . The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 85:15 to $60: 40$ ) affording $\mathbf{1 0 s}(31.1 \mathrm{mg}, 59.1 \mu \mathrm{~mol}, 59 \%$ ) as off-white amorphous solid.
TLC: $\mathrm{R}_{\mathrm{f}}=0.41\left(\mathrm{SiO}_{2}, 1: 1\right.$ pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.56-7.51(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.38$ -7.31 (m, 6H, ArH), 7.24-7.19 (m, 2H, ArH), 7.08-7.04 (m, 2H, ArH), 6.99-6.91 (m, 3H, ArH), 5.18 (d, $\left.J=12.3 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArCH}_{2} \mathrm{O}\right), 5.10\left(\mathrm{~d}, J=12.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCH}_{2} \mathrm{O}\right), 4.17(\mathrm{t}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH})$, $3.70\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.67\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.28\left(\mathrm{dd}, J=10.5,7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.90(\mathrm{dd}, J=8.3,2.3 \mathrm{~Hz}$, $2 \mathrm{H}, \mathrm{CH}_{2}$ ), $2.82\left(\mathrm{~d}, \mathrm{~J}=10.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.63-2.56\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.15(\mathrm{dd}, J=10.5,7.7 \mathrm{~Hz}, 1 \mathrm{H}$, $\left.\mathrm{CH}_{2}\right) .{ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 202.4,172.2,172.0,171.7,145.0,137.5,135.8,132.8,128.6,128.6$, 128.4, 128.2, 128.15, 128.12, 126.4, 125.8, 67.2, 59.3, 52.9, 52.8, 49.1, 48.3, 45.7, 42.5, 34.6, 31.0. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 2953 (w), 1729 (s), 1724 (s), 1676 (m), 1450 (m), 1262 (s), 1214 (s), 1213 (s), 1108 (m), $912(\mathrm{~m})$. HRMS (ESI/QTOF) m/z: [M + H] ${ }^{+}$Calcd for $\mathrm{C}_{32} \mathrm{H}_{31} \mathrm{O}_{7}{ }^{+} 527.2064$; Found 527.2072

## Unsuccessful substrates:

- Cyclopropanes


Full conversion, Trace of product observed


Full conversion, Trace of product observed


Decomposition

- BCBs

n.r.

n.r.

n.r.


To a solution of $\mathbf{1 0 h}(444 \mathrm{mg}, 1.00 \mathrm{mmol}, 1.00$ equiv) in $\mathrm{MeOH}(4 \mathrm{~mL})$ was added a solution of LiOH ( $96.0 \mathrm{mg}, 4.00 \mathrm{mmol}, 4.00$ equiv, in $4 \mathrm{~mL} \mathrm{H} \mathrm{H}_{2} \mathrm{O}$ ). The mixture was stirred at room temperature for 7 hours. Upon full conversion of $\mathbf{1 0 h}$ as indicated by TLC analysis, the mixture was concentrated under vacuo, followed by quenching with solution of $\mathrm{HCl} 1 \mathrm{M}(10 \mathrm{~mL})$. $\mathrm{Et}_{2} \mathrm{O}$ was added for extraction. The aqueous layer was then extracted with $\operatorname{DCM}(3 \times 5 \mathrm{~mL})$. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated under reduced pressure to yield product 12 ( $422 \mathrm{mg}, 0.980 \mathrm{mmol}, 98 \%$ yield) as a white solid. The diastereomeric ratio was determined by integrating the NMR signals of ArCOCH 4.65 ppm (major), 4.50 ppm (minor) in the isolated mixture (dr. >95:5). The NMR data is reported for the major diastereoisomer.
TLC: $\mathrm{R}_{\mathrm{f}}=0.19\left(\mathrm{SiO}_{2}\right.$, Pentane:EtOAc 3:1, few drops of $\left.\mathrm{Et}_{3} \mathrm{~N}\right)$. Mp: $215.3-217.7^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H}$ NMR (400 $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ). 9.71 (br, 1H, COOH), $7.66-7.59(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.45-7.36(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.27(\mathrm{~d}, \mathrm{~J}=8.1$ $\mathrm{Hz}, 2 \mathrm{H}, \operatorname{ArH}$ ), $6.97-6.88(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH}), 6.68-6.58(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 4.65(\mathrm{dd}, \mathrm{J}=10.1,6.5 \mathrm{~Hz}, 1 \mathrm{H}$, ArCOCH), 3.73 (s, 3H, $\mathrm{CO}_{2} \mathrm{CH}_{3}$ ), 3.32 (dd, $J=15.3,10.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCHCH}_{2}$ ), 3.24 (dd, $J=10.7,8.2$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), $3.08-2.95\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right.$ ), $2.81(\mathrm{~d}, J=10.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}$ ) , $2.74(\mathrm{~d}, \mathrm{~J}=10.6 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CCH}_{2}$ ), 2.55 (dd, $\left.\left.J=15.3,6.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCHCH}\right)_{2}\right){ }^{13} \mathrm{C}^{\mathrm{C}} \mathrm{NMR}$. $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right.$ ) 201.4, 175.9, 171.7, 160.51 (d, $J=245.3 \mathrm{~Hz}), 137.1,133.2,130.64(\mathrm{~d}, J=14.8 \mathrm{~Hz}$ ), 128.9, 128.84, 128.76, 128.22 (d, $J=$ 29.9 Hz ), 124.05 (d, $J=3.2 \mathrm{~Hz}$ ), 115.21 (d, $J=21.3 \mathrm{~Hz}$ ), 72.1, 53.1, 52.7, 45.5, 44.8, 44.5, 38.9, 34.9. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2979 (m), 2358 (w), 1737 ( s$), 1680(\mathrm{~m}), 1492$ (m), 1450 (m), 1321 (m), 1224 (s), 1118 (m), 809 (w), 760 (s). HRMS (ESI/QTOF) m/z: [M - H] Calcd for $\mathrm{C}_{23} \mathrm{H}_{19} \mathrm{ClFO}_{5}{ }^{-} 429.0911$; Found 429.0910 .

1-Methyl
2-((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl) 4-benzoyl-2-chloro-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2dicarboxylate (13)


To a solution of 12 ( $44.0 \mathrm{mg}, 0.100 \mathrm{mmol}, 1$ equiv), estrone ( $40.5 \mathrm{mg}, 0.150 \mathrm{mmol}, 1.50$ equiv), and 4$\mathrm{N}, \mathrm{N}$-dimethylaminopyridine ( $0.6 \mathrm{mg}, 0.05 \mathrm{mmol}, 0.05$ equiv) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \mathrm{~mL}), \mathrm{N}, \mathrm{N}$ diisopropylcarbodiimide ( $18.7 \mathrm{mg}, 0.150 \mathrm{mmol}, 1.50$ equiv.) was added in one portion. The resulting solution was stirred at it overnight. The volatile solvent was evaporated under reduced pressure and the crude product was purified by chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient pentane/ethyl acetate $10: 1$ to 2:1). To afford product 13 ( $27.4 \mathrm{mg}, 0.0402 \mathrm{mmol}, 40 \%$ yield) as off-white amorphous solid. The diastereomeric ratio was determined by integrating the NMR signals of ArCOCH 4.72 ppm (major), 4.64 ppm (minor) in the isolated mixture (dr. $>95: 5$ ). The NMR data is reported for the major diastereoisomer.

TLC: $\mathrm{R}_{\mathrm{f}}=0.5\left(\mathrm{SiO}_{2}\right.$, Pentane:EtOAc 70:30). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.68-7.62(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.45$ - 7.39 (m, 1H, ArH), 7.30 (dd, J=13.7, 8.2 Hz, 3H, ArH), $7.00-6.89$ (m, 5H, ArH), $6.67-6.59$ (m, 1H, ArH), 4.72 (dd, $J=10.4,6.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 3.74 (s, $3 \mathrm{H}, \mathrm{CO}_{2} \mathrm{CH}_{3}$ ), 3.41 (dd, $J=15.2,10.5 \mathrm{~Hz}, 1 \mathrm{H}$, ArCOCHCH$)_{2}$, 3.32 (dd, $J=10.7,8.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 3.08 (ddd, $J=10.6,8.3,4.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.94 (dt, $J=9.0,3.6 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{H}$-estrone), $2.86-2.76(\mathrm{~m}, 2 \mathrm{H}, 2 \mathrm{xCCH}$ ), $2.63(\mathrm{dd}, J=15.3,6.4 \mathrm{~Hz}, 1 \mathrm{H}$, ArCOCHCH2), $2.56-2.48$ (m, 1H, H-estrone), 2.42 (dd, $J=10.6,4.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}$-estrone), 2.30 (dt, $J=$ $10.9,6.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}$-estrone), 2.19 - 2.11 (m, 1H, H-estrone), 2.06 - 1.93 (m, 3H, H-estrone), 1.64 1.58 (m, 3H, H-estrone), 1.52 - 1.46 (m, 2H, H-estrone), 1.27 - 1.23 (m, 1H, H-estrone) 0.92 (s, 3H, $\mathrm{CCH}_{3}$ ). ${ }^{13} \mathrm{C}$ NMR. 221.0, 201.4, 171.4, $169.6(\mathrm{~d}, \mathrm{~J}=3.1 \mathrm{~Hz}), 160.4(\mathrm{~d}, \mathrm{~J}=245.4 \mathrm{~Hz}), 148.6,138.2$, $137.8,137.1,133.3,130.52(\mathrm{~d}, J=15.1 \mathrm{~Hz}), 128.8,128.4,128.1(\mathrm{~d}, J=33.8 \mathrm{~Hz}), 126.5,123.9(\mathrm{~d}, J=$ $3.2 \mathrm{~Hz}), 121.2,118.3,115.13$ (d, $J=21.1 \mathrm{~Hz}), 112.8,72.3,53.1,52.5,50.5,48.0,45.3,44.8,44.7,44.2$, 38.9, 38.0, 35.9, 34.8, 31.6, 29.4, 26.3, 25.8, 21.6, 13.9. Signal of one ketone is unresolved or overlapped with signal 201.4 ppm. ${ }^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$-115.5. IR $\left(\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}\right) 2935(\mathrm{w}), 2254$ (w), 1736 (s), 1678 (m), 1493 (m), 1451 (m), 1221 (s), 912 (m). HRMS (ESI/QTOF) m/z: [M + H] ${ }^{+}$Calcd for $\mathrm{C}_{41} \mathrm{H}_{41} \mathrm{ClFO}_{6}{ }^{+} 683.2570$; Found 683.2568 .

2-(4-((2S,3R)-1-(4-fluorophenyl)-3-((S)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-oxoazetidin-2-yl)phenyl) 1methyl 4-benzoyl-2-chloro-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2-dicarboxylate (14)


To a solution of 12 ( $44.0 \mathrm{mg}, 0.100 \mathrm{mmol}$, 1 equiv), Ezetimibe ( $40.9 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.00$ equiv), and 4-N,N-dimethylaminopyridine ( $0.6 \mathrm{mg}, 0.05 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \mathrm{~mL}), \mathrm{N}, \mathrm{N}$ '-diisopropylcarbodiimide (DIC, $18.7 \mathrm{mg}, 0.150 \mathrm{mmol}$ ) was added in one portion. The resulting solution was stirred at rt overnight. The volatile solvent was evaporated under reduced pressure and the crude product was purified by chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient pentane/ethyl acetate 10:1 to 2:1) to afford product 14 (67.9 $\mathrm{mg}, 0.0840 \mathrm{mmol}, 84 \%$ yield) as a white solid. The diastereomeric ratio was determined by integrating the NMR signals of $\mathrm{CCH}_{2} 2.81 \mathrm{ppm}$ (major), 2.74 ppm (minor) in the isolated mixture ( $\mathrm{dr}>95: 5$ ). The NMR data is reported for the major diastereoisomer.

TLC: $\mathrm{R}_{\mathrm{f}}=0.39\left(\mathrm{SiO}_{2}\right.$, Pentane:EtOAc 60:40). Mp: $103-105{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.66-$ 7.61 (m, 2H, ArH), 7.42 (t, J=7.3 Hz, 1H, ArH), $7.39-7.35$ (m, 2H, ArH), $7.33-7.26$ (m, 4H, ArH), $7.25-7.22$ (m, 4H, ArH), 7.03 (td, $J=8.7,2.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $6.97-6.87$ (m, 5H, ArH), 6.64 (ddd, $J=$ $11.0,7.6,1.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 4.75-4.68$ (m, 2H, $\operatorname{ArCOCH}, \operatorname{ArCHOH}$ ), 4.65 (d, $J=2.4 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArCHNCO}$ ), 3.73 (d, $J=2.5 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CO}_{2} \mathrm{CH}_{3}$ ), 3.42 (dd, $J=15.2,10.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{COCHCH}_{2}$ ), 3.33 (ddd, $J=10.4,8.2$, $1.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 3.08 (dddd, $J=14.9,10.5,7.6,4.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CCH}_{2}$ and $\mathrm{COCHCH}_{2}$ ), 2.81 (d, $J=10.6$ $\mathrm{Hz}, 2 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.63 (dd, $J=15.2,6.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{COCHCH}_{2}$ ), $2.04-1.97\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2}\right), 1.96-$ $1.89\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR (101 MHz, $\left.\mathrm{CDCl}_{3}\right)$ ס. 201.5, 201.4, 171.5, 169.7, 167.4, 162.4 (d, $J=245.7 \mathrm{~Hz}$ ), 160.5 (d, $J=245.3 \mathrm{~Hz}$ ), 159.2 (d, $J=243.7 \mathrm{~Hz}$ ), 151.0, 140.1 (d, $J=3.3 \mathrm{~Hz}$ ), 137.1, $135.7,133.8$ (d, $J=2.9 \mathrm{~Hz}), 130.5$ (d, $J=14.9 \mathrm{~Hz}), 133.3,128.9(\mathrm{~d}, J=8.1 \mathrm{~Hz}), 128.7(\mathrm{~d}, J=5.1 \mathrm{~Hz})$, 128.4, 128.1, $127.5(\mathrm{~d}, J=8.0 \mathrm{~Hz}), 124.1(\mathrm{~d}, J=3.1 \mathrm{~Hz}), 122.4(\mathrm{~d}, J=2.9 \mathrm{~Hz}), 118.5(\mathrm{~d}, J=7.8 \mathrm{~Hz})$, $116.1(\mathrm{~d}, \mathrm{~J}=22.5 \mathrm{~Hz}$ ), $115.6(\mathrm{~d}, J=21.4 \mathrm{~Hz}), 115.4,115.2,73.3,72.4,61.0,60.6,53.4,52.7,45.4$, 44.9, 44.6, 38.9, 36.7, 35.0, 25.2. ${ }^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl} 3$ ) $\delta-114.8(\mathrm{~d}, J=2.7 \mathrm{~Hz}$ ), $-115.5(\mathrm{~d}, J=$
2.6 Hz ), -117.8 (d, $J=7.4 \mathrm{~Hz}$ ). IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) $3490(\mathrm{w}), 2952(\mathrm{w}), 2251(\mathrm{w}), 1735(\mathrm{~s}), 1677(\mathrm{~m}), 1509$ (s), 1450 (m), 1387 (m), 1220 (s), 911 (m), 836 (m), 733 (s). HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $\mathrm{C}_{47} \mathrm{H}_{40} \mathrm{ClF}_{3} \mathrm{NO}_{7}^{+} 822.2440$; Found 822.2412.

Methyl 4-benzoyl-2-chloro-5-(2-fluorophenyl)-2-
(methoxy(methyl)carbamoyl)bicyclo[3.1.1]heptane-1-carboxylate (15)


To a solution of 12 ( $44.0 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.00$ equiv), N -methoxymethylamine hydrochloride ( 19.5 mg , $0.200 \mathrm{mmol}, 2.00$ equiv), and $4-\mathrm{N}, \mathrm{N}$-dimethylaminopyridine ( $0.6 \mathrm{mg}, 0.05 \mathrm{mmol}, 0.5$ equiv.) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ $(2 \mathrm{~mL}), \mathrm{N}, \mathrm{N}$-diisopropylcarbodiimide (DIC, $18.7 \mathrm{mg}, 0.150 \mathrm{mmol}$ ) was added in one portion. The resulting solution was stirred at it overnight. The volatile solvent was evaporated under reduced pressure and the crude product was purified by chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient pentane/ethyl acetate $2: 1$ to $1: 1$ ) to afford product $15(37.4 \mathrm{mg}, 79.1 \mu \mathrm{~mol}, 79 \%)$ as white solid. TLC: $\mathrm{R}_{\mathrm{f}}=0.26\left(\mathrm{SiO}_{2}, 1: 1\right.$ Pentane:Et $\left.\mathrm{t}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.65-7.57(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.43-7.33$ (m, 1H, ArH), $7.23(\mathrm{t}, \mathrm{J}=7.8 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{ArH}), 6.92-6.83(\mathrm{~m}, 3 \mathrm{H}, \mathrm{ArH}), 6.61-6.51(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 4.64$ (dd, $J=10.3,6.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), $3.81\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.67\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.23\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{NCH}_{3}\right), 3.05$ (ddd, $J=10.4,7.8,4.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 2.95 (dd, $J=10.6,5.4 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}$ ), $2.86-2.77\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right.$ ), 2.45 (d, $\left.J=10.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ס 201.9, 172.8, 170.1, 160.6 (d, J = 245.2 Hz ), 137.4, $133.0,130.76(\mathrm{~d}, J=8.1 \mathrm{~Hz}), 129.02(\mathrm{~d}, J=5.3 \mathrm{~Hz}), 128.6(\mathrm{~d}, J=8.1 \mathrm{~Hz}), 128.3,128.0$, 123.98 (d, $J=3.2 \mathrm{~Hz}$ ), 115.08 (d, $J=21.4 \mathrm{~Hz}$ ), 70.8, 61.1, 52.3, 52.1, 45.7, 44.2 (d, $J=3.3 \mathrm{~Hz}$ ), 43.9, 36.9, 34.0, 33.1. IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 3521 (w), 2950 (m), 1733 (m), 1654 (s), 1452 (m), 1368 (m), 1317 (m), 1186 (s), 964 (m), 755 (s). HRMS (ESI/QTOF) m/z: [M + H $]^{+}$Calcd for $\mathrm{C}_{25} \mathrm{H}_{26} \mathrm{CIFNO}_{5}{ }^{+} 474.1478$; Found 474.1488.

## 4-Benzoyl-2-chloro-5-(2-fluorophenyl)-1-(phenylcarbamoyl)bicyclo[3.1.1]heptane-2-carboxylic acid (16)



Following a reported procedure, ${ }^{20}$ to an oven-dried vial equipped with a stirring bar was added 12 (44.0 $\mathrm{mg}, 0.100 \mathrm{mmol}, 1.00$ equiv) and aniline ( $11.0 \mathrm{mg}, 0.120 \mathrm{mmol}, 1.20$ equiv) under $\mathrm{N}_{2}$ atmosphere. Toluene ( 0.25 M ) was added, then LiHMDS ( 1.0 M in THF, $0.200 \mathrm{~mL}, 2.0$ equiv) was added while vigorous stirring at room temperature, the reaction was stirred at room temperature until full conversion of starting material as indicated by TLC. After that, the reaction mixture was quenched with $\mathrm{NH}_{4} \mathrm{Cl}$ (sat.) until $\mathrm{pH}<7$, and extracted with $\mathrm{Et}_{2} \mathrm{O}(2 \times 10 \mathrm{~mL})$, the organic layer was washed with water ( $1 \times 10 \mathrm{~mL}$ ), brine ( $1 \times 10 \mathrm{~mL}$ ), dried and concentrated. The crude mixture was purified by chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient pentane/ethyl acetate 2:1 to 1:2) to afford product 16 ( $32.9 \mathrm{mg}, 67.0 \mu \mathrm{~mol}, 67 \%$ ) as white amorphous solid. TLC: $\mathrm{R}_{\mathrm{f}}=0.15\left(\mathrm{SiO}_{2}, 1: 1\right.$ Pentane: $\left.\mathrm{Et}_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H} \mathbf{N M R}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.54$
(s, 1H, COOH), 7.72 - 7.65 (m, 2H, ArH), $7.49-7.43$ (m, 3H, ArH), $7.36-7.27$ (m, 4H, ArH), 7.15 7.07 (m, 2H, ArH), $7.05-6.94$ (m, 2H, ArH), 6.58 (ddd, $J=11.4,7.7,1.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 4.40 (td, $J=$ $6.8,3.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCH}$ ), 3.06 (dd, $J=10.4,3.6 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArCOCHCH}_{2}$ ), $3.02-2.98$ (m, 1H, ArCOCHCH$)_{2}$, $2.97-2.90\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.86\left(\mathrm{dt}, J=14.1,3.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.57(\mathrm{dd}, J=12.9,6.4$ $\left.\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 201.5,176.4,168.6,161.0(\mathrm{~d}, \mathrm{~J}=244.9 \mathrm{~Hz}), 137.3(\mathrm{~d}, \mathrm{~J}=$ 20.0 Hz ), 133.0, 129.2, 129.1, 129.0, 128.98, 128.4, 128.2, 126.6 (d, $J=14.8 \mathrm{~Hz}), 125.3,124.2(\mathrm{~d}, J=$ $3.1 \mathrm{~Hz}), 120.6,115.21(\mathrm{~d}, J=22.4 \mathrm{~Hz}), 76.2,60.3,54.0(\mathrm{~d}, J=4.6 \mathrm{~Hz}), 52.5,49.4,43.1,37.9$. $^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$-111.2. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) $3410(\mathrm{w}), 3399(\mathrm{w}), 3062(\mathrm{~m}), 1704(\mathrm{~s}), 1679(\mathrm{~s}), 1599(\mathrm{~m})$, 1529 (s), 1495 (m), 1443 (s), 1224 (s), 737 (s). HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $\mathrm{C}_{28} \mathrm{H}_{24} \mathrm{CIFNO}_{4}{ }^{+} 492.1372$; Found 492.1383 .

Trimethyl 5-(4-chlorophenyl)-4-(hydroxy(phenyl)methyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate (17)



17, 42\%, dr > 95:5
To an oven dried vessel, the starting material $101(24.2 \mathrm{mg}, 0.0500 \mathrm{mmol}, 1.00$ equiv.) was added together with (S)-(-)-2-Methyl-CBS-oxazaborolidine ( $2.8 \mathrm{mg}, 0.010 \mathrm{mmol}, 0.20$ equiv.). The flask was filled with $\mathrm{N}_{2}$ and anhydrous THF ( 0.1 M ) was added. At $0^{\circ} \mathrm{C}$, a borane-dimethyl sulfide complex solution ( $2.00 \mathrm{M}, 20 \mu \mathrm{~L}, 0.040 \mathrm{mmol}, 0.80$ equiv.) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched by slow addition of methanol at $0^{\circ} \mathrm{C}$. The solution was concentrated and partitioned between water and DCM. The aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to obtain the crude alcohol that was further purified by flash column chromatography (Biotage, gradient pentane:EtOAc, 100:0 to 60:40) to afford pure trimethyl 5-(4-chlorophenyl)-4-(hydroxy(phenyl)methyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate 17 ( $10 \mathrm{mg}, 0.020$ $\mathrm{mmol}, 42 \%$ ) as a colorless oil. Only one diastereomer was isolated.

TLC: $\mathrm{R}_{\mathrm{f}}=0.44\left(\mathrm{SiO}_{2}, 70: 30\right.$ pentane:EtOAc). ${ }^{1} \mathrm{H}$ NMR ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.29-7.18(\mathrm{~m}, 5 \mathrm{H}$, ArH), $7.15-7.11(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 7.07-7.02(\mathrm{~m}, 2 \mathrm{H}, \operatorname{ArH}), 4.51(\mathrm{~d}, \mathrm{~J}=7.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHOH}), 3.75(2 \mathrm{x} \mathrm{s}$, $6 \mathrm{H}, \mathrm{OCH}_{3}$ x2), $3.67\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right.$ ), 2.82 (dd, $J=10.5,7.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $2.64\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CCH}_{2}+\right.$ CHCHOH), 2.50 (dd, $J=10.5,1.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.37 (dd, $J=14.8,7.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.16 (dd, $J=$ 14.8, $9.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 2.02 (dd, $J=10.5,7.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ). ${ }^{13} \mathrm{C} \mathrm{NMR}^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.7,172.6,171.5,145.8,142.2,132.4,128.8,128.4,127.6,127.2,126.8,76.4,59.2,53.0,52.5$, 49.4, 48.3, 44.4, 43.9, 34.3, 31.2, 29.8. IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 3532 (w), 2953 (w), 1730 (s), 1497 (w), 1436 (m), 1267 (s), 1210 (m), 1094 (m), 1054 (w), 1015 (w), 914 (m). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{26} \mathrm{H}_{27} \mathrm{ClNaO}_{7}{ }^{+}$509.1338; Found 509.1337.

Trimethyl (E)-5-(4-chlorophenyl)-4-((2-(2,4-dinitrophenyl)hydrazineylidene)(phenyl)methyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (19a)


101

$\mathrm{EtOH}(0.05 \mathrm{M}), 80^{\circ} \mathrm{C}$


19a
Following a reported procedure, ${ }^{17}$ one drop of sulfuric acid was added to a solution of $10 \mathrm{I}(48.4 \mathrm{mg}$, 0.100 mmol ) and 2,4-dinitrophenylhydrazine $18(19.8 \mathrm{mg}, 0.800 \mathrm{mmol})$ in EtOH ( 2 mL ). The resultant mixture was heated to $80^{\circ} \mathrm{C}$ and stirred for 16 hours. Then the resulting mixture was quenched with sat. aq. sodium bicarbonate and extracted with ethyl acetate ( $3 \times 5 \mathrm{~mL}$ ). The organic layer was dried with anhydrous sodium sulfate, filtrated and concentrated under reduced pressure. The crude product was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 85:15 to $60: 40$ ) to afford product 19 a ( $47.2 \mathrm{mg}, 0.0711 \mathrm{mmol}, 71 \%$ ) as red solid. Recrystallization was performed in pentane/DCM ( 1 mL of pentane and few drops of DCM was added until solid was dissolved completely) for X-Ray analysis.

TLC: $\mathrm{R}_{\mathrm{f}}=0.31\left(\mathrm{SiO}_{2}, 70: 30\right.$ pentane:EtOAc). Mp: 215-217 ${ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 11.01(\mathrm{~s}$, $1 \mathrm{H}, \mathrm{NH}$ ), 9.04 (d, $J=2.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 8.37 (ddd, $J=9.5,2.6,0.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.96 (d, $J=9.6 \mathrm{~Hz}$, 1H, ArH), $7.44-7.28$ (m, 3H, ArH), $7.20-7.08$ (m, 2H, ArH), $6.93-6.82$ (m, 2H, ArH), $6.69-6.58$ (m, $2 \mathrm{H}, \mathrm{ArH}$ ), $3.85\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.73\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.45(\mathrm{t}, \mathrm{J}=8.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{N}=\mathrm{C}-$ CH), 3.35 (dd, $J=10.3,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}$ ), 3.17 (dd, $J=8.6,1.9 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{NCCHCH}_{2}$ ), 2.81 (d, $J=10.7$ $\left.\mathrm{Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 2.62\left(\mathrm{dd}, J=10.4,1.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right), 1.96\left(\mathrm{dd}, J=10.7,7.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CCH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.6,172.4,171.3,159.6,144.7,144.1,138.1,134.2,132.5,130.3,130.2,129.7$, 129.5, 128.6, 127.4, 126.0, 123.6, 116.1, 59.3, 53.3, 53.2, 52.7, 51.1, 48.3, 46.0, 43.4, 34.4, 33.7. IR $\left(\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}\right) 3292$ (w), 1731 (m), 1617 (s), 1591 (m), 1519 (m), 1426 (m), 1336 (s), 1271 (m), 1135 (m). HRMS (Nanochip-based ESI/LTQ-Orbitrap) m/z: [M + H $]^{+}$Calcd for $\mathrm{C}_{32} \mathrm{H}_{30} \mathrm{CIN}_{4} \mathrm{O}_{10}{ }^{+} 665.1645$; Found 665.1647.

## Crystal data of 8

 CCDC number 2238001Crystal Data and Experimental



Experimental. Single clear intense yellow irregularshaped crystals of tin-02-104-2-p were used as supplied. A suitable crystal with dimensions $0.14 \times 0.13 \times 0.06 \mathrm{~mm}^{3}$ was selected and mounted on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at a steady $T=199.99(10) \mathrm{K}$ during data collection. The structure was solved with the ShelXT (Sheldrick, 2015) solution program using dual methods and by using Olex2 1.5 (Dolomanov et al., 2009) as the graphical interface. The model was refined with ShelXL 2018/3 (Sheldrick, 2015) using full matrix least squares minimisation on $\boldsymbol{F}^{\mathbf{2}}$.

Crystal Data. $\mathrm{C}_{32} \mathrm{H}_{29} \mathrm{ClN}_{4} \mathrm{O}_{10}, M_{r}=665.04$, triclinic, $P-1$ (No. 2), $\quad \mathrm{a}=10.4389(4) \AA, \quad \mathrm{b}=11.2944(4) \AA, \quad \mathrm{c}=$ 15.7957(4) $\AA, \quad \alpha=91.844(3)^{\circ}, \quad \beta=100.856(3)^{\circ}, \quad \gamma=$ $109.065(4)^{\circ}, V=1719.84(11) \AA^{3}, T=199.99(10) \mathrm{K}, Z=2$, $Z^{\prime}=1, \mu\left(\mathrm{Cu} \mathrm{K}_{\alpha}\right)=1.496,14274$ reflections measured, 6628 unique $\left(\mathrm{R}_{\text {int }}=0.0195\right)$ which were used in all calculations. The final $w R_{2}$ was 0.1047 (all data) and $R_{1}$ was 0.0370 ( $\mathrm{I} \geq 2$ $\sigma(\mathrm{I})$ ).
$R_{1}=3.70 \%$

| Compound | tin-02-104-2-p |
| :---: | :---: |
| Formula | $\mathrm{C}_{32} \mathrm{H}_{29} \mathrm{ClN}_{4} \mathrm{O}_{10}$ |
| $D_{\text {calc. }} / \mathrm{g} \mathrm{cm}^{-3}$ | 1.284 |
| $\mu / \mathrm{mm}^{-1}$ | 1.496 |
| Formula Weight | 665.04 |
| Colour | clear intense yellow |
| Shape | irregular-shaped |
| Size/mm ${ }^{3}$ | $0.14 \times 0.13 \times 0.06$ |
| T/K | 199.99(10) |
| Crystal System | triclinic |
| Space Group | $P-1$ |
| $a / \AA$ | 10.4389(4) |
| $b / \AA$ | 11.2944(4) |
| $c / \AA$ | 15.7957(4) |
| $\alpha /{ }^{\circ}$ | 91.844(3) |
| $\beta /{ }^{\circ}$ | 100.856(3) |
| $\gamma /{ }^{\circ}$ | 109.065(4) |
| $\mathrm{V} / \AA^{3}$ | 1719.84(11) |
| Z | 2 |
| $Z^{\prime}$ | 1 |
| Wavelength/Å | 1.54184 |
| Radiation type | $\mathrm{Cu} \mathrm{K}{ }_{\alpha}$ |
| $\Theta_{\text {min }} /{ }^{\circ}$ | 2.863 |
| $\Theta_{\max } /{ }^{\circ}$ | 72.992 |
| Measured Refl's. | 14274 |
| Indep't Refl's | 6628 |
| Refl's I $\geq 2$ (I) | 5578 |
| $R_{\text {int }}$ | 0.0195 |
| Parameters | 511 |
| Restraints | 0 |
| Largest Peak | 0.339 |
| Deepest Hole | -0.401 |
| GooF | 1.031 |
| $w R_{2}$ (all data) | 0.1047 |
| $w_{2}$ | 0.0991 |
| $R_{1}$ (all data) | 0.0443 |
| $R_{1}$ | 0.0370 |

## Preliminary mechanistic studies

## A. Cyclic Voltammetry measurements

Cyclic voltammetry (CV) experiments were performed using a BioLogic Potentiostat SP-150. All experiments were carried out under an atmosphere of dinitrogen in degassed and anhydrous acetonitrile solution containing TBAPF $_{6}(0.1 \mathrm{M})$. The setup consisted of a Pt surface as a working electrode, a Pt wire as the counter electrode, and an Ag wire coated with AgCl in 3 M KCl as a reference electrode. The recorded voltammograms have been referenced to the internal standard $\mathrm{Fc} / \mathrm{Fc}^{+}$ (ferrocene/ferrocenium) couple.


Figure S1 Cyclic voltammograms of Fc (3 cycles)


Figure S2 Cyclic voltammograms of 1b at $100 \mathrm{mVs}^{-1}$ (3 cycles)
Comment figure S2: The results of the CV measurement of $\mathbf{1 b}$ show that a reduction peak about -2.31 V vs. $\mathrm{Fc} / \mathrm{Fc}^{+}$was observed. The reduction process is irreversible.

Based on previous report, ${ }^{18}$ estimated redox potential can be converted following below equation:
$\mathrm{V}_{\mathrm{SCE}}=\mathrm{V}_{\mathrm{Fc}+} / 0+0.4=-1.91 \mathrm{~V}$ vs SCE
Comparing potential of 1b: $\mathrm{E}_{1 \mathrm{~b}}=-1.91 \mathrm{~V}$ vs SCE with PC5 $\left(\mathrm{E}_{1 / 2}{ }^{\mathrm{PC}}{ }^{*} \mathrm{PC}+=-0.96 \mathrm{~V}\right.$ vs SCE; $\mathrm{E}_{1 / 2}{ }^{\mathrm{PC}}$ +PC$=+0.66 \mathrm{~V}$ vs SCE), ${ }^{19}$ the electron transfer process to $\mathbf{1 b}$ by PC5 can be excluded.


Figure S3 Cyclic voltammograms of 3a at $100 \mathrm{mVs}^{-1}$ (3 cycles)
Comment: There is no significant signal observed for 3a showing that the oxidation of 3a by PC5 is not possible

## B. Kinetic studies

Following the method of two-step process described in literature. ${ }^{21}$
In a $12^{*} 75 \mathrm{~mm}$ borosilicate glass tube were added the photocatalyst ( $1.0 \mathrm{~mol} \%$ ) and $\mathbf{1 b}$ ( 1.0 equiv, $100 \mu \mathrm{~mol}, 26 \mathrm{mg}$ ). The tube was closed with a rubber septum and sealed off with parafilm. Three cycles of evacuate-refill with nitrogen were performed to remove $\mathrm{O}_{2}$ and extra-dry MeOD in a sealed-cap bottle was added with alkyne 3a in different ratio (Table belove) under nitrogen atmosphere. A fan was used for cooling purposes. NMR conversion was determined by adding 1.0 equiv. of benzylbenzoate as internal standard, the ArCOCH signal was used to determine conversion.

| Graph | 3a $(\mathrm{mL})$ | MeOD $(\mathrm{mL})$ | Concentration 3a (M) | Ratio 1b/3a |
| :---: | :---: | :---: | :---: | :---: |
| 1 | 0.5 | 1.5 | 2.279411765 | $1: 45$ |
| 2 | 0.3 | 1.7 | 1.367647059 | $1: 27$ |
| 3 | 0.2 | 1.8 | 0.911764706 | $1: 18$ |





According to two-step process reported literature: ${ }^{21}$

- The three graphs show good linear fit of $\ln [\mathbf{1 b}]$ vs time, therefore, the reaction is $1^{\text {st }}$ order in 1b
- Since the $-K_{\text {obs }}$ (or slope) of three graphs are constant $\sim 0,00245$. the reaction is Zero order in 3a


## C. Quantum yield

The quantum yield of the reaction was determined using the procedure reported previously based on mol of photon flux using standard ferrioxalate actinometry. ${ }^{22}$

$$
\begin{equation*}
\phi=\frac{\text { mol of formed product }}{\text { mol of photon flux } \cdot t \cdot F} \tag{1}
\end{equation*}
$$

$\phi$ : quantum yield , $\mathrm{t}:$ time of reaction ( s ) , F : incident light absorbed by the reaction mixture

$$
F=1-10^{-A}
$$

A is the absorbance of the reaction mixture at 436 nm which is the known wavelength of $\phi$ ferrioxalate. In addition, reported wavelength 436 nm chosen was close to our reaction condition at 440 nm . The absorbance of the reaction mixture $(0.1 \mathrm{M} \mathrm{1b}$, 2 equiv. of $\mathbf{3 a}, 1 \mathrm{~mol} \%$ of PC5 in MeOH ) was measured in a cuvette equipped with a Teflon-coated magnetic stirring bar after mixing for 30 seconds in dark. The experiments were repeated twice for average value.


The absorbances were recorded at 430 nm were $\sim 1.50$, therefore, $\mathrm{A}=0.968$

## Photon flux measurement:

Based on a reported procedure, ${ }^{22 a}$ the following solutions were prepared using black flasks wrapped in aluminum foil and stored in the dark at room temperature:

Solution 1: Ferrioxalate solution ( 0.15 M ): Potassium ferrioxalate hydrate ( $1.31 \mathrm{~g}, 3.00 \mathrm{mmol}$ ) was added to a black flask wrapped in aluminum foil containing $\mathrm{H}_{2} \mathrm{SO}_{4}(20 \mathrm{~mL}, 0.05 \mathrm{M})$. The flask was stirred for complete solvation of the green solid in complete darkness. It is noted that the solution should be in a completely darkness with the laboratory light switched off.

Solution 2: 1,10-Phenanthroline ( $50 \mathrm{mg}, 277.8 \mu \mathrm{~mol}$ ) and $\mathrm{NaOAc}(11.25 \mathrm{~g}, 137.2 \mathrm{mmol}$ ) were added to a flask containing $\mathrm{H}_{2} \mathrm{SO}_{4}(50 \mathrm{~mL}, 0.5 \mathrm{M})$ and sonicated until the solution becomes homogeneous.

First step is to measure the absorbance of the non-irradiated solution: the buffered solution 2 ( $350 \mu \mathrm{~L}$ ) was added to 2.0 mL of solution 1 in a cuvette that had been covered with aluminum foil in completely dark, all lights are switched off. The cuvette was allowed to rest for 1 h , then
immediately measure absorbance with caution of any light incidence. The data was recorded at 510 nm to be 0.456 of average three determinations (dark 1,2,3)

Second step is to record the absorbance of the irradiated sample. Solution $1(2.0 \mathrm{~mL})$ was added to a cuvette equipped with a stirring bar, then irradiated with stirring for 90 s at $\lambda=440 \mathrm{~nm}$. After irradiation, $350 \mu \mathrm{~L}$ of solution 2 was added to the cuvette, then allowed to rest for 1 h in the complete darkness. The data was recorded at 510 nm to be 2.327 of average three determinations (light 1,2,3)


After that, photon flux value was determined using reported equation.

$$
\begin{align*}
& {\left[\mathrm{Fe}\left(\mathrm{C}_{2} \mathrm{O}_{4}\right) \mathrm{n}\right]^{+(3-2 \mathrm{n})} \rightarrow \mathrm{Fe}^{2+}+(\mathrm{n}-1)\left(\mathrm{C}_{2} \mathrm{O}_{4}\right)^{2-}+\mathrm{C}_{2} \mathrm{O}_{4}^{-} \text {(under light) } } \\
& {\left[\mathrm{Fe}\left(\mathrm{C}_{2} \mathrm{O}_{4}\right) \mathrm{n}\right]^{+(3-2 \mathrm{n})}+\mathrm{C}_{2} \mathrm{O}_{4}^{-} \rightarrow \mathrm{Fe}^{2+}+\mathrm{n}\left(\mathrm{C}_{2} \mathrm{O}_{4}\right)^{2-}+2 \mathrm{CO}_{2} \text { (no light) } }  \tag{3}\\
& \mathrm{mol}\left(\mathrm{Fe}^{2+}\right)=\frac{V . \Delta A}{l . \epsilon}=3.96 .10^{-7} \quad(\mathrm{~mol}) \tag{4}
\end{align*}
$$

V : total volume of solution ( 0.00235 I ),
$\Delta A$ is different of absorbance between dark and light experiment $=2.327-0.456=1.871$
I : path length $(1.0 \mathrm{~cm})$.
$\epsilon$ is the molar absorptivity at $510 \mathrm{~nm}\left(11110 \mathrm{~L} \mathrm{~mol}^{-1} \mathrm{~cm}^{-1}\right) .{ }^{22}$

$$
\begin{equation*}
\text { Photon flux }=\frac{\operatorname{mol}\left(F e^{2+}\right)}{\phi\left(F e^{2+}\right) \cdot t \cdot F}=4.50 \cdot 10^{-9} \text { einstein }^{-1} \tag{5}
\end{equation*}
$$

$\phi\left(F e^{2+}\right)$ : quantum yield for the ferrioxalate actinometer (1.01 at $\left.\lambda=436 \mathrm{~nm}\right),{ }^{22 \mathrm{c}}$
t: reaction time 90 seconds
F : incident light absorbed by the reaction mixture $=0.968$

## Quantum yield calculation

The reaction gave $19 \%$ of product formed after 180 minutes based on kinetic studies.

$$
\phi=\frac{\text { mol of formed product }}{\text { mol of photon flux } \cdot t \cdot F}=\frac{1 \cdot 9 \cdot 10^{-5}}{4.50 \cdot 10^{-9} \cdot 180 \cdot 60 \cdot 0.968}=0.403
$$

## D. UV-VIS spectrum and Fluorescence quenching

- The absorption spectrum was determined in MeOH for 1 a ( 0.04 M ), 3a ( 0.04 M ) and mixture of $\mathbf{1 a}+\mathbf{3 a}(0.04 \mathrm{M})$
- Stern-Volmer quenching: A stock solution of PC5 ( 0.05 mM ) was prepared and added to three cuvettes with screw cap in an inert atmosphere. 1a, 3a and mixture of 1a+3a were used as different quenchers in each cuvette. The data were recorded at different concentration of quenchers $(0,0.016 \mathrm{M}, 0.048 \mathrm{M}, 0.08 \mathrm{M}, 0.112 \mathrm{M})$






## E. NMR analysis of interaction

The NMR spectrum was measured with solution of $0.1 \mathrm{mmol} \mathbf{1 b}(26.2 \mathrm{mg})$ in 0.75 mL of $\mathrm{CD}_{3} \mathrm{CN}$. Each time, styrene 4 a was added with $0.05 \mathrm{mmol}, 0.05 \mathrm{mmol}, 0.1 \mathrm{mmol}, 0.2 \mathrm{mmol}, 0.4 \mathrm{mmol}$ corresponding to the ratio $\mathbf{1 b}: \mathbf{4 a} 1: 0.5 ; 1: 1 ; 1: 2 ; 1: 4 ; 1: 8$. All NMR were calibrated with the signal of $\mathrm{CD}_{3} \mathrm{CN}$ at 1.97 ppm . Similar protocol was used for $\mathbf{1 b}-\mathbf{6}$ complex (Figure S5)


Figure S4-1b-4a complex


Figure S5-1b-6h complex

## F. Control experiments



Following general procedure E, starting from $\mathbf{1 b}$ ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) in the absence of trapping reagents in $\mathrm{MeOH}(1 \mathrm{~mL})$. The reaction mixture was stirred for 48 h under irradiation with a 440 nM Kessil lamp. The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 85:10 to 70:30) affording a mixture of $\mathbf{1 b a}+\mathbf{1 b b}(10.1 \mathrm{mg}, 0.038 \mathrm{mmol}, 38 \%)$. The ratio ( $57: 43 \mathbf{1 b a}: 1 \mathbf{b b}$ ) is determined from the isolated mixture on the signal of $\mathrm{ArCOCH} \mathbf{1 b a} 3.09 \mathrm{ppm}$, 1bb 2.75 ppm .
(1ba) ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.94$ (d, J=7.8 Hz, 2H, ArH), 7.57-7.54 (m, 1H, ArH), 7.49 7.45 (m, 2H, ArH), $3.74\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.57\left(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCO}_{2} \mathrm{Me}\right), 3.09(\mathrm{t}, J=7.2 \mathrm{~Hz}$, $2 \mathrm{H}, \mathrm{ArCOCH} 2$ ), 2.38 - 2.33 (m, 2H, $\mathrm{ArCOCH}_{2} \mathrm{CH}_{2}$ ). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{14} \mathrm{H}_{16} \mathrm{NaO}_{5}{ }^{+}$287.0890; Found 287.0891. Data matching reported value. ${ }^{23}$
(1bb) ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.09$ (ddd, $J=7.8,1.6,0.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), $7.57-7.54$ (m, 1H, ArH), $7.45-7.38(\mathrm{~m}, 2 \mathrm{H}, \operatorname{ArH}), 3.81\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.82-2.68\left(\mathrm{~m}, 4 \mathrm{H}, 2 \mathrm{CH} \mathrm{CH}_{2}\right.$ ). HRMS (ESI/QTOF) m/z: [M + Na] ${ }^{+}$Calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{NaO}_{5}{ }^{+}$285.0733; Found 285.0736.

## G. Direct excitation experiments

Following general procedure E, starting from 1b or $\mathbf{1 a}$ ( $0.100 \mathrm{mmol}, 1.0$ equiv.) and $\mathbf{3 a}$ ( 0.500 mmol, 5 equiv.) in $\mathrm{CH}_{3} \mathrm{CN}(1 \mathrm{~mL})$ in absent of catalyst. The reaction mixture was stirred for 48 h with the indicated lamps. The yield was determined by NMR with benzyl benzoate (1 equiv) as standard, the signal of ArCOCH was integrated.

|  <br> 1 a |  |  |  |
| :---: | :---: | :---: | :---: |
| Entry | Light source | R | NMR yield (\%) |
| 1 | 365 (Rayonnet) | Me | 8 |
| 2 | 365 (Rayonnet) | $\mathrm{CO}_{2} \mathrm{Me}$ | 6 |
| 3 | 390 Kessil lamp | Me | 57 |
| 4 | 390 Kessil lamp | $\mathrm{CO}_{2} \mathrm{Me}$ | 60 |
| 3 | 440 Kessil lamp | Me | 0 |
| 4 | 440 Kessil lamp | $\mathrm{CO}_{2} \mathrm{Me}$ | 0 |

## H. Radical trapping experiment

Tempo trapping experiment

## Dimethyl 2-(3-oxo-3-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)malonate (1bc)



Following general procedure E, starting from $\mathbf{1 b}(26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and TEMPO ( $78.0 \mathrm{mg}, 0.500 \mathrm{mmol}, 5.0$ equiv.), in $\mathrm{CH}_{3} \mathrm{CN}(1 \mathrm{~mL})$. The reaction mixture was stirred for 48 h under irradiation with a 440 nm Kessil lamp. The crude mixture was purified by column chromatography on Biotage $\left(\mathrm{SiO}_{2}\right.$, gradient of pentane:diethyl ether from 85:10 to 70:30) affording 1bc ( $5.4 \mathrm{mg}, 0.011 \mathrm{mmol}, 11 \%$ ) as yellow sticky oil.
TLC: $\mathrm{R}_{\mathrm{f}}=0.29\left(\mathrm{SiO}_{2}, 3: 1\right.$ Pentane:Et $\left.{ }_{2} \mathrm{O}\right) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.10-8.01(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH})$, $7.61-7.54(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 7.47$ (dd, $J=8.4,7.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 5.06$ (dd, $J=9.6,4.0 \mathrm{~Hz}, 1 \mathrm{H}$, ArCHON), 3.67 (d, $J=2.0 \mathrm{~Hz}, 6 \mathrm{H}, \mathrm{OCH}_{3}$ ), 3.43 (dd, $J=9.3,5.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{MeO}_{2} \mathrm{CCH}$ ), 2.69 (td, $J$ $=9.5,4.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $2.54\left(\mathrm{ddd}, J=14.3,9.7,5.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 1.51-1.24(\mathrm{~m}, 9 \mathrm{H}$, $\mathrm{CH}_{3}$ and $\mathrm{CH}_{2}$ Tempo), 1.17 (s, $3 \mathrm{H}, \mathrm{CH}_{3}$ Tempo), 1.03 (s, 3H, $\mathrm{CH}_{3}$ Tempo), 0.83 (s, 3H, $\mathrm{CH}_{3}$ Tempo). ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ) $\delta$ 200.8, 169.5, 169.3, 136.1, 133.5, 129.4, 128.7, 85.2, 60.3, 60.0, 52.8, 52.7, 47.5, 40.5 (2 Carbons TEMPO), 34.0 33.9, 31.3, 20.4, 17.2 (2 Carbons TEMPO). IR ( $\mathrm{v}_{\text {max }} \mathrm{cm}^{-1}$ ) 3003 ( w ), 2937 (m), 1754 ( s$), 1739$ (s), 1685 (m), 1440 (m), 1262 ( s$)$, 1241 (s), 1240 (s), 1155 (s). HRMS (ESI/QTOF) m/z: [M + H] ${ }^{+}$Calcd for $\mathrm{C}_{23} \mathrm{H}_{34} \mathrm{NO}_{6}{ }^{+} 420.2381$; Found 420.2385.

## Radical trapping experiments with DMPO



Following general procedure E, starting from $\mathbf{1 b}(26.2 \mathrm{mg}, 0.100 \mathrm{mmol}, 1.0$ equiv.) and DMPO ( $56.5 \mathrm{mg}, 0.500 \mathrm{mmol}, 5.0$ equiv.), in $\mathrm{CH}_{3} \mathrm{CN}(1 \mathrm{~mL})$. The reaction mixture was stirred for 48 h under Kessil lamp 440. The crude mixture was purified by column chromatography on Biotage ( $\mathrm{SiO}_{2}$, gradient of pentane:diethyl ether from $50: 50$ to 0:100) affording a mixture of 1bd + 1be ( 15.4 $\mathrm{mg}, 41.1 \mu \mathrm{~mol}, 41 \%$ ). The ratio (1bd : 1be $45: 55$ was determined by NMR of crude mixture 5.10 ppm (1bd, ArCOCH) and 3.22 ppm (1be, ArCOCH)

The same reaction was performed in the presence of $\mathbf{3 a}$ ( $51 \mathrm{mg}, 0.50 \mathrm{mmol}, 5.0$ equiv.) affording a mixture of 1bd + 1be ( $18.2 \mathrm{mg}, 48.5 \mu \mathrm{~mol}, 49 \%$ ). $\mathbf{1 b d}$ : 1be $48: 52$

TLC: $\mathrm{R}_{\mathrm{f}}=0.25\left(\mathrm{SiO}_{2}, \mathrm{Et}_{2} \mathrm{O}\right)$.
(1bd) ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.08$ - 8.02 (m, 2H, ArH), 7.58 - 7.53 (m, 1H, ArH), 7.48 7.43 (m, 2H, ArH), 5.10 (dd, $J=8.1,6.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArCOCHON}), 3.75\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.72(\mathrm{~s}, 3 \mathrm{H}$, $\left.\mathrm{OCH}_{3}\right), 3.41\left(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHCO}_{2} \mathrm{Me}\right), 2.68-2.63\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}\right), 2.61-2.53\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right.$ DMPO,), 2.34 - 2.27 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{CHCH}_{2}$ ), $2.24-2.14$ ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{DMPO}$ ), 1.93 (ddd, $J=12.8,9.2$, $6.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{DMPO}$ ), 1.82 (ddd, $J=13.1,9.2,4.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{DMPO}$ ), 1.41 (s, 3H, DMPO $\mathrm{CH}_{3}$ ), 1.16 (s, 3H, DMPO CH $)_{3}$ ) ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) 196.7, 169.5, 169.3, 139.4, 135.5, 134.1, 129.0 128.5, 74.3, 53.0, 52.9, 49.4, 43.7, 32.2, 26.9, 25.6, 24.63, 24.62.
(1bd) ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.92$ - 7.87 (m, 2H, ArH, 7.58 - 7.53 (m, 1H, ArH), 7.48 $7.43(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 3.70\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.22\left(\mathrm{t}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArCOCH}_{2}\right), 2.86(\mathrm{t}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}$, DMPO CH2), $2.70\left(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArCOCH}_{2} \mathrm{CH}_{2}\right), 2.02\left(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{DMPO} \mathrm{CH}_{2}\right), 1.30(\mathrm{~s}$, $6 \mathrm{H}, \mathrm{DMPO} \mathrm{CH}_{3}$ ). ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) 199.1, 168.4 (two $\mathrm{CO}_{2} \mathrm{Me}$ ), 140.1, 136.7, 133.2, 128.7, 128.3, 73.9 (two $\mathrm{OCH}_{3}$ ), 58.5, 53.2, 34.3, 33.0, 27.4, 27.1, 25.0 (two $\mathrm{CH}_{3}$ DMPO),

IR ( $\mathrm{v}_{\text {max }}, \mathrm{cm}^{-1}$ ) 2953 (m), 2931 (m), 2928 (m), 1739 (s), 1685 (s), 1681 (s), 1580 (m), 1244 (s), 1214 (s), 1151 (m). HRMS (ESI/QTOF) m/z: [M + H] ${ }^{+}$Calcd for $\mathrm{C}_{20} \mathrm{H}_{26} \mathrm{NO}_{6}{ }^{+} 376.1755$; Found 376.1750 .

The same reaction with DMPO was performed with 1a

(nanochip-ESI) m/z: $[\mathrm{M}+\mathrm{Na}]^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{25} \mathrm{NNaO}_{2}{ }^{+}$310.1777; Found 310.1767 (APCI) m/z: $[\mathrm{M}+\mathrm{H}]^{+}$Calcd for $\mathrm{C}_{18} \mathrm{H}_{26} \mathrm{NO}_{2}{ }^{+}$288.1958; Found 288.1962.


## IR experiment to investigate the role of $(\mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}$

A solution of $\mathbf{1 a}(0.1 \mathrm{M})$ in $\mathrm{CH}_{3} \mathrm{CN}$. Then ( PhO$)_{2} \mathbf{P O}_{2} \mathrm{H}$ was added in 0.3 equiv., 1 equiv. and 1.5 equiv. to record the IR. We observed the intensity of $\mathrm{C}=\mathrm{O}$ signal is weaken when increasing the amount of $(\mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}$





A solution of $11 \mathrm{~h}(0.1 \mathrm{M})$ in $\mathrm{CH}_{3} \mathrm{CN}$. Then ( PhO$)_{2} \mathrm{PO}_{2} \mathrm{H}$ was added in 0.3 equiv., 1 equiv. and 1.5 equiv. to record the IR. We observed the intensity of $\mathrm{C}=\mathrm{O}$ signal is weaken when increasing the amount of $(\mathrm{PhO})_{2} \mathrm{PO}_{2} \mathrm{H}$


A solution of $1 \mathbf{a}(0.1 \mathrm{M})$ in $\mathrm{CH}_{3} \mathrm{CN}$. Then 3 a was added in 2 equiv, and 4 equiv. to record the IR. A solution of $\mathbf{1 a}(0.1 \mathrm{M})$ in $\mathrm{CH}_{3} \mathrm{CN}$. We observed the intensity of $\mathrm{C}=\mathrm{O}$ signal remained unchanged


## Computational Details.

Geometries of all species were optimized at the M06 ${ }^{24,25} /$ def2-SVP ${ }^{26}$ level using the SMD implicit solvent model ${ }^{27}$ (methanol) in Gaussian16. ${ }^{28}$ For the photocatalysts (PC1-PC5) vertical excitation energies (from the optimized $S_{0}$ state) for the $S_{1}$ and low-lying triplet states ( $\mathrm{T}_{1}-\mathrm{T}_{5}$ ) were determined at the M06/TZP ${ }^{29}$ level using the Tamm-Dancoff approximation (which improves the description of the triplet excitation energies ${ }^{30}$ ) as implemented in the ADF software. ${ }^{31,32}$ Values reported in the manuscript also include the influence of solvent (methanol) using the COSMO solvation model. ${ }^{33}$

Free energy profiles were determined first by optimizing structures on either the S 0 or T 1 potential energy surfaces at the M06/def2-SVP level using the SMD solvent model in Gaussian16. Species were characterized as either minima (zero imaginary frequencies) or transition state (one imaginary frequency) by examining the vibrational frequencies. Single point energies were then computed on the M06/def2-SVP geometries at the M06/TZP level using the COMSO solvation model in ADF. Free energy corrections were determined using the quasi rigid-rotor harmonical oscillator model ${ }^{34}$ and corrected for translational entropy in solution ${ }^{35}$ using the approach of Matin, Hay, and $\operatorname{Pratt}^{36}$ ( $24.69 \mathrm{~mol} / \mathrm{L}$ for methanol) using Goodvibes. ${ }^{37,38}$ Reported free energies are taken as the sum of the M06/TZP electronic energies and the M06/def2-SVP free energy corrections.

Table S1. TDDFT vertical excitation energies computed at the M06/TZVP//M06/def2-SVP level in implicit methanol solvent (COSMO) for photocatalysts PC1-PC5. Values in $\mathrm{kcal} / \mathrm{mol}$.

| Species | $\mathbf{S}_{\mathbf{1}}$ | $\mathbf{T}_{\mathbf{1}}$ | $\mathbf{T}_{\mathbf{2}}$ | $\mathbf{T}_{\mathbf{3}}$ | $\mathbf{T}_{\mathbf{4}}$ | $\mathbf{T}_{\mathbf{5}}$ |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: |
| PC1 | 83.0 | 64.3 | 80.0 | 81.5 | 82.3 | 88.4 |
| PC2 | 82.0 | 62.9 | 80.0 | 81.0 | 82.2 | 87.6 |
| PC3 | 65.8 | 51.6 | 64.8 | 65.3 | 69.6 | 76.0 |
| PC4 | 48.3 | 44.5 | 48.2 | 56.9 | 58.2 | 62.4 |
| PC5 (methanol) | 65.8 | 65.2 | 68.7 | 69.7 | 74.1 | 77.1 |
| PC5 (gas phase) | 55.1 | 54.5 | 66.5 | 67.4 | 69.8 | 70.2 |

Table S2. Spin-orbit couplings between the S1 excited state and low-lying triplet states for PC5. Computations at the M06/TZVP//M06/def2-SVP level in implicit methanol solvent (COSMO). Values in $\mathrm{cm}^{-1}$.

| Excited State | $\mathbf{T}_{1}$ | $\mathbf{T}_{\mathbf{2}}$ | $\mathbf{T}_{3}$ | $\mathbf{T}_{4}$ | $\mathbf{T}_{\mathbf{5}}$ |
| :--- | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{S}_{1}$ | 33.04 | 13.35 | 46.77 | 745.95 | 1126.10 |

Table S3. Electronic, free energy correction, single point energies, total free energies (all in Hartree) and relative free energies (compared to Int1-Triplet, in $\mathrm{kcal} / \mathrm{mol}$ ) of relevant species. See computational details for further information.

|  | M06/def2-SVP <br> Electronic <br> Energy | M06/def2-SVP <br> Free Energy <br> Correction | M06/TZP <br> Electronic <br> Energy | Total Free <br> Energy | Relative <br> Free <br> Energy |
| :--- | :---: | :---: | :---: | :---: | :---: |
| phenylacetylene | -307.927291 | 0.084609 | -3.950437 | -3.865828 | -- |
| Int1-Singlet | -540.372535 | 0.197205 | -7.170251 | -6.973046 | -69.75 |
| Int1-Triplet | -540.254913 | 0.192054 | -7.053941 | -6.861887 | 0.00 |
| TS1,2-Triplet | -540.008545 | 0.186219 | -7.044779 | -6.858560 | 2.09 |
| Int2-Triplet | -540.050137 | 0.185924 | -7.087209 | -6.901285 | -24.72 |


| Int3-Triplet | -847.987360 | 0.284606 | -11.044410 | -10.759804 | -20.14 |
| :--- | :---: | :---: | :---: | :---: | :---: |
| TS3,4-Triplet | -847.985115 | 0.286958 | -11.037859 | -10.750901 | -14.55 |
| Int4-Triplet | -848.039810 | 0.292358 | -11.088415 | -10.796057 | -42.89 |
| Int5-Singlet | -848.154319 | 0.300298 | -11.202441 | -10.902143 | -109.46 |

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## NMR spectra

(2,2-Dimethylcyclopropyl)(phenyl)methanone (1a)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


## (2,2-Dimethylcyclopropyl)(4-methoxyphenyl)methanone (1f):

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


## (2,2-Dimethylcyclopropyl)(4-methoxyphenyl)methanone (1g):

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



## Trans-phenyl(2-phenylcyclopropyl)methanone (1j) :

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )




${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Phenyl((1R,2R)-2-(trifluoromethyl)cyclopropyl)methanone (1k)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13}$ C NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


## ${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



Phenyl(spiro[2.5]octan-1-yl)methanone (1I):
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Phenyl(spiro[2.3]hexan-1-yl)methanone (1m):
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


## (2,2-Dimethylcyclopropyl)(naphthalen-2-yl)methanone (1n):

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )




## Dimethyl 2-(4-bromobenzoyl)cyclopropane-1,1-dicarboxylate (1q):

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 2-(4-fluorobenzoyl)cyclopropane-1,1-dicarboxylate (1r) :
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )




${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


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Dimethyl 2-(4-methoxybenzoyl)cyclopropane-1,1-dicarboxylate (1s):
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13}$ C NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 2-([1,1'-biphenyl]-4-carbonyl)cyclopropane-1,1-dicarboxylate (1t):
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 2-(dibenzo[b,d]furan-2-carbonyl)cyclopropane-1,1-dicarboxylate (1u):
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )






## Methyl 2-benzoyl-1-chlorocyclopropane-1-carboxylate (1v):

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13}$ C NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


## Methyl 2-benzoyl-1-fluorocyclopropane-1-carboxylate (1w) :

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


## Methyl 2-benzoyl-(1-estrone)-cyclopropane-1-carboxylate (1x):

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )




## (2-(((3-(naphthalen-1-yl)prop-2-yn-1-yl)oxy)methyl)cyclopropyl)(phenyl)methanone (6a)

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


## (2-((cinnamyloxy)methyl)cyclopropyl)(phenyl)methanone (6b)

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )




${ }^{13} \mathrm{C}$ NMR


Cyclobutane-1,2-diyl)bis(phenyImethanone) (8)
NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )





## (4,4-dimethyl-2-phenylcyclopent-2-en-1-yl)(phenyl)methanone (2a)

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 4-benzoyl-3-phenylcyclopent-2-ene-1,1-dicarboxylate (2b)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 4-(4-(methoxycarbonyl)benzoyl)-3-phenylcyclopent-2-ene-1,1-dicarboxylate (2c) ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

(4,4-difluoro-2-phenylcyclopent-2-en-1-yl)(phenyl)methanone (2d)
${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )




[^0]${ }^{19} \mathbf{F} \mathbf{N M R}\left(376 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$
$\qquad$
(4,4-dimethyl-2-phenylcyclopent-2-en-1-yl)(o-tolyl)methanone 2e ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

(4,4-dimethyl-2-phenylcyclopent-2-en-1-yl)(4-methoxyphenyl)methanone 2f ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



## (4,4-dimethyl-2-phenylcyclopent-2-en-1-yl)(4-fluorophenyl)methanone 2g

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^1]${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


| -70 | -75 | -80 | -85 | -90 | -95 | -100 | -105 | -110 | -115 | -120 | -125 | -130 | -135 | $-1^{\text {c }}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |

(4,4-dimethyl-2-phenylcyclopent-2-en-1-yl)(4-(trifluoromethyl)phenyl)methanone (2h)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )





[^2]${ }^{19}$ F NMR $\left(376 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$



## Tert-butyl 4-benzoyl-3-phenylcyclopent-2-ene-1-carboxylate 2i

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ )


## (2,4-diphenylcyclopent-2-en-1-yl)(phenyl)methanone 2j

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Phenyl(2-phenyl-4-(trifluoromethyl)cyclopent-2-en-1-yl)methanone (2k)
Major diastereomer ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Major diastereomer ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



$\qquad$

Minor diastereomer, (orange is the impurity from major diastereomer).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )




Minor diastereomer, ${ }^{13} \mathbf{C} \mathbf{N M R}$ ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) (orange is the impurity from major diastereomer).

${ }^{19}$ F NMR $\left(376 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$




Phenyl(3-phenylspiro[4.5]dec-3-en-2-yl)methanone (2I)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^3]Phenyl(7-phenylspiro[3.4]oct-7-en-6-yl)methanone 2m ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

(4,4-dimethyl-2-phenylcyclopent-2-en-1-yl)(naphthalen-2-yl)methanone 2n ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


|  <br>  |
| :---: |



| ?10 | 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

phenyl(3-phenylspiro[4.5]dec-3-en-2-yl)methanone 20
${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


(2-(4-methoxyphenyl)-4,4-dimethylcyclopent-2-en-1-yl)(phenyl)methanone 2p ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

(2-(4-bromophenyl)-4,4-dimethylcyclopent-2-en-1-yl)(phenyl)methanone 2q ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 3-([1,1'-biphenyl]-4-yl)-4-benzoylcyclopent-2-ene-1,1-dicarboxylate 2 r ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 4-benzoyl-3-(4-methoxyphenyl)cyclopent-2-ene-1,1-dicarboxylate 2s
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $\mathbf{1 0 1} \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

:10

Dimethyl 4-benzoyl-3-(4-chlorophenyl)cyclopent-2-ene-1,1-dicarboxylate 2t
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 4-benzoyl-3-(4-(methoxycarbonyl)phenyl)cyclopent-2-ene-1,1-dicarboxylate 2u ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13}$ C NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )




[^4]Dimethyl 4-benzoyl-3-(thiophen-3-yl)cyclopent-2-ene-1,1-dicarboxylate 2v
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^5]3-Ethyl 1,1-dimethyl 4-benzoylcyclopent-2-ene-1,1,3-tricarboxylate (2w)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



Dimethyl 3-acetyl-4-benzoylcyclopent-2-ene-1,1-dicarboxylate (2x)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



## (4,4-dimethyl-2-phenylcyclopentyl)(phenyl)methanone 4a

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Blue : Major diastereomer, Orange: minor diastereomer.

${ }^{13} \mathrm{C}$ NMR ( $\mathbf{1 0 1} \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 3-benzoyl-4-phenylcyclopentane-1,1-dicarboxylate (4b) (major diastereoisomer)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $\mathbf{1 0 1} \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



Dimethyl 3-benzoyl-4-phenylcyclopentane-1,1-dicarboxylate 4b (minor diastereoisomer)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13}$ C NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


## (4,4-dimethyl-2-phenylcyclopentyl)(4-methoxyphenyl)methanone (4c)

${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Blue : major diastereomer, Orange : minor diastereomer.

${ }^{13} \mathbf{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )
$\stackrel{\circ}{\circ}$



210
$200 \quad 19$
$\begin{array}{lll}0 & 180 & 17\end{array}$
140
$30 \quad 120$
100
$\mathrm{f} 1(\mathrm{ppm})$

## (4,4-Dimethyl-2-phenylcyclopentyl)(4-(trifluoromethyl)phenyl)methanone (4d)

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): Blue major diastereomer, orange minor diastereomer

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^6]Tert-butyl 4-benzoyl-3,3-diphenylcyclopentane-1-carboxylate (4e)
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ) Blue : major diastereomer, orange : minor diastereomer

${ }^{13} \mathbf{C}$ NMR (101 MHz, $\left.\mathrm{CDCl}_{3}\right)$

| $\begin{gathered} \stackrel{n}{i n} \\ \stackrel{\sim}{1} \end{gathered}$ | $\stackrel{\tilde{N}}{\underset{\sim}{\mid}}$ |  |  <br>  |  | $\begin{gathered} \text { m } \\ 0.0 \\ i \\ i \end{gathered}$ | $\stackrel{\sim}{3}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |




[^7](4-Methyl-2,2-diphenylcyclopentyl)(phenyl)methanone (4f)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Major diastereomer

${ }^{3} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Minor diastereomer

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^8]
## (2,2-diphenyl-4-(trifluoromethyl)cyclopentyl)(phenyl)methanone (4g)

${ }^{1} \mathbf{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Blue major diastereomer, orange minor diastereomer

${ }^{3} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



${ }^{19}$ F NMR $\left(376 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$



(2,2-Diphenylcyclopentyl)(phenyl)methanone (4h)
${ }^{1} \mathbf{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



Dimethyl 4-benzoyl-3,3-diphenylcyclopentane-1,1-dicarboxylate (4i)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$


[^9]Dimethyl 3-acetyl-4-benzoylcyclopentane-1,1-dicarboxylate (4j1)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Major diastereomer



${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



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[^10]${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): Minor diastereomer

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



Trimethyl 4-benzoylcyclopentane-1,1,3-tricarboxylate (4k1)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Major diastereomer

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



[^11]${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right.$ minor diastereomer.

${ }^{13} \mathbf{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$



[^12]Dimethyl 3-benzoyl-4-(trimethylsilyl)cyclopentane-1,1-dicarboxylate (4I)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) Blue: Major diastereomer, Orange : minor diastereomer.

${ }^{13}$ C NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 4-benzoyl-3,3-diethylcyclopentane-1,1-dicarboxylate (4k)
${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )
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Dimethyl 4-benzoyl-3-methyl-3-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (4n) ${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ) (4n1) Major

${ }^{13} \mathbf{C} \operatorname{NMR}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$
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[^13](4n2) Minor ${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 3-benzoyl-4-(2-oxopyrrolidin-1-yl)cyclopentane-1,1-dicarboxylate 40
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ), Blue: major diastereomer, Orange: minor diastereomer.


${ }^{13} \mathbf{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$







Dimethyl 3-benzoyl-4-(1,3-dioxoisoindolin-2-yl)cyclopentane-1,1-dicarboxylate 4p ${ }^{1} \mathbf{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) 2p1 Major

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^14]${ }^{1} \mathbf{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ) 2 p2 Minor

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 3-benzoyl-4-(thiophen-2-yl)cyclopentane-1,1-dicarboxylate (4q)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Blue major diastereomer, orange minor diastereomer

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${ }^{13} \mathrm{C}$ NMR (101 MHz, $\left.\mathrm{CDCl}_{3}\right)$


[^15]Dimethyl 3-(benzofuran-2-yl)-4-benzoylcyclopentane-1,1-dicarboxylate (4r)
${ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) Blue major diastereomer, orange minor diastereomer

${ }^{13} \mathbf{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )
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[^17]Dimethyl 8-benzoylspiro[3.4]octane-6,6-dicarboxylate (4s)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^18](6-(naphthalen-1-yl)-3,3a,4,5-tetrahydro-1H-cyclopenta[c]furan-5-yl)(phenyl)methanone (7a)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) Blue major diastereomer, orange minor diastereomer

${ }^{13} \mathbf{C} \operatorname{NMR}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$
Noc



Phenyl(4-phenylhexahydro-1H-cyclopenta[c]furan-5-yl)methanone (7b)
${ }^{1} \mathbf{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) 7b1

${ }^{13} \mathbf{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$



(7b2) ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )






7b3 ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


7b4 ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$


## (2,3,4,5-tetrahydro-[1,1'-biphenyl]-2,5-diyl)bis(phenyImethanone) (9a)

${ }^{1} \mathbf{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Blue major diastereomer, orange: minor diastereomer

${ }^{13} \mathbf{C}$ NMR ( $201 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


(4'-methoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2,5-diyl)bis(phenylmethanone) (9b)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Blue major diastereomer, orange: minor diastereomer

${ }^{13} \mathbf{C}$ NMR ( $201 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


## 4,4-dimethyl-2-phenylcyclopentan-1-ol (4da)

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR $\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$

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| 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  |  |  |  |  | f1 (ppm) |  |  |  |  |  |  |  |  |  |  |

Trimethyl 4-benzoyl-5-phenylbicyclo[3.1.1]heptane-1,2,2-tricarboxylate 10a
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



Trimethyl 4-(4-bromobenzoyl)-5-phenylbicyclo[3.1.1]heptane-1,2,2-tricarboxylate 10b ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )
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Trimethyl 4-(4-fluorobenzoyl)-5-phenylbicyclo[3.1.1]heptane-1,2,2-tricarboxylate 10c ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Trimethyl 4-(4-methoxybenzoyl)-5-phenylbicyclo[3.1.1]heptane-1,2,2-tricarboxylate 10d ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $\mathbf{1 0 1} \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


2-(Tert-butyl) 1-methyl 4-benzoyl-5-phenylbicyclo[3.1.1]heptane-1,2-dicarboxylate 10e ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )
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Trimethyl 4-benzoyl-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate 10f ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13}$ C NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )




${ }^{19} \mathrm{~F}$ NMR $\left(376 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$

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Trimethyl 4-([1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate 10 g

## ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

$\qquad$


Trimethyl 4-(dibenzo[b,d]furan-2-carbonyl)-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate 10h
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



Dimethyl 4-benzoyl-2-chloro-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2-dicarboxylate 10i . Blue: major diastereomer, Orange: minor diastereomer.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $201 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



Dimethyl 4-benzoyl-2-fluoro-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2-dicarboxylate 10j. Blue: major diastereomer, Orange: minor diastereomer.

${ }^{13} \mathrm{C}$ NMR (101 MHz, CDCl3)


${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^20]Dimethyl4-benzoyl-5-(2-fluorophenyl)-2-(((13S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)bicyclo[3.1.1]heptane-1,2-dicarboxylate 10k
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$


${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

 f1 (ppm)

Trimethyl 4-benzoyl-5-(4-chlorophenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate 10 I ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Trimethyl 4-benzoyl-5-(4-(trifluoromethyl)phenyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate 10 m
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13}$ C NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



Trimethyl 4-benzoyl-5-(4-(methoxycarbonyl)phenyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate 10n
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Trimethyl 4-benzoyl-5-(4-(trifluoromethoxy)phenyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate 100
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13}$ C NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

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| 10 | 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |



## HMBC



Trimethyl 4-benzoyl-5-(3-methoxyphenyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate 10p ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


| 10 | 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |

Trimethyl 4-benzoyl-5-(m-tolyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate 10q ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


$!10$

1-allyl 2,2-dimethyl 4-benzoyl-5-(4-chlorophenyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate 10 r
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )





1-benzyl 2,2-dimethyl-4-benzoyl-5-phenylbicyclo[3.1.1]heptane-1,2,2-tricarboxylate (10s) ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


4-Benzoyl-2-chloro-5-(2-fluorophenyl)-1-(methoxycarbonyl)bicyclo[3.1.1]heptane-2-carboxylic acid (12)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^21]${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



1-Methyl 2-((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl) 4-benzoyl-2-chloro-5-(2-
fluorophenyl)bicyclo[3.1.1]heptane-1,2-dicarboxylate (13) ${ }^{1} \mathrm{H} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$

${ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^22]${ }^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )



2-(4-((2S,3R)-1-(4-fluorophenyl)-3-((S)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-oxoazetidin-2yl)phenyl) 1-methyl 4-benzoyl-2-chloro-5-(2-fluorophenyl)bicyclo[3.1.1]heptane-1,2-dicarboxylate (14) - Blue: major diastereomer, Orange: minor diastereomer.

## ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


${ }^{13} \mathrm{C}$ NMR ( $\mathbf{1 0 1} \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

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| -109 | 110 | 1 | 112 | 1 | 11 |  |  |  |  |  |  |  | 1 |  |  |  |
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| -109 | -110 | -111 | -112 | -113 | -114 | -115 | -116 | $\begin{gathered} -117 \\ \mathrm{f} 1(\mathrm{ppm}) \end{gathered}$ | -118 | -119 | -120 | -121 | -122 | -123 | -124 | 125 |

Methyl 4-benzoyl-2-chloro-5-(2-fluorophenyl)-2-
(methoxy(methyl)carbamoyl)bicyclo[3.1.1]heptane-1-carboxylate (15)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^23]4-Benzoyl-2-chloro-5-(2-fluorophenyl)-1-(phenylcarbamoyl)bicyclo[3.1.1]heptane-2-carboxylic acid (16) ${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ )


## 



$\begin{array}{lllllllllll}3.3 & 3.2 & 3.1 & 3.0 & 2.9 & \begin{array}{llllll}2.8 & 2.7 & 2.6 & 2.5 & 2.4 & 2.3 \\ & & & & & f(\mathrm{ppm})\end{array} & & & & \end{array}$

${ }^{13} \mathbf{C} \operatorname{NMR}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$
$-201.50$

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| 210 | 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 10 | 20 | 10 |
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|  |  |  |  |  |  |  |  |  |  | f1 (ppm) |  |  |  |  |  |  |  |  |  |  |

Trimethyl 5-(4-chlorophenyl)-4-(hydroxy(phenyl)methyl)bicyclo[3.1.1]heptane-1,2,2tricarboxylate (17):
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


ROESY


Trimethyl (E)-5-(4-chlorophenyl)-4-((2-(2,4-
dinitrophenyl)hydrazineylidene)(phenyl)methyl)bicyclo[3.1.1]heptane-1,2,2-tricarboxylate (19a)
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


Dimethyl 2-(3-oxo-3-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)malonate (1bc) ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

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No
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## Radical trapping experiments with DMPO

${ }^{1}$ H NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : Blue : 1bd, Orange: 1be

${ }^{13} \mathbf{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

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$\begin{array}{lllllllllllll}230 & 220 & 210 & 200 & 190 & 180 & 170 & 160 & 150 & 140 & 130 & 120 & 110 \\ & & & & (\mathrm{ppm})\end{array}$


[^0]:    

[^1]:    

[^2]:    

[^3]:    210
    $200 \quad 190$

    - 170

    60
    140
    120 $110 \begin{gathered}100 \\ \mathrm{f} 1 \\ (\mathrm{ppm})\end{gathered}$

[^4]:    10
    $\begin{array}{lllll}200 & 190 & 180 & 170 & 160\end{array}$
    $\begin{array}{llllll}150 & 140 & 130 & 120 & \begin{array}{c}110 \\ f 1(\mathrm{ppm})\end{array} & 100\end{array}$

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[^6]:    

[^7]:    

[^8]:    

[^9]:    $\begin{array}{llllllllllllllllllllllllllllllllllll}200 & 190 & 180 & 170 & 160 & 150 & 140 & 130 & 120 & 110 & 100 & 90 & 80 & 70 & 60 & 50 & 40 & 30 & 20 & 10 & 0\end{array}$

[^10]:    $\begin{array}{llllllllllll}230 & 220 & 210 & 200 & 190 & 180 & 170 & 160 & 150 & 140 & 130 & 120 \\ f 1(\mathrm{ppm})\end{array}$

[^11]:    $\begin{array}{lllllllllllll}230 & 220 & 210 & 200 & 190 & 180 & 170 & 160 & 150 & 140 & 130 & 120 & 110 \\ \text { f1 (ppm) }\end{array}$

[^12]:    

[^13]:    

[^14]:    

[^15]:    

[^16]:    

[^17]:    $200 \quad 1$
    $190 \quad 180 \quad 170$
    $170 \quad 160 \quad 1$ $150 \quad 140$ $130 \quad 120$ $10 \begin{gathered}100 \\ \text { f1 (ppm) }\end{gathered}$

[^18]:    $\begin{array}{lllllllllllll}230 & 220 & 210 & 200 & 190 & 180 & 170 & 160 & 150 & 140 & 130 & 120 & 110 \\ & & & & & & & & & & \text { f(ppm) }\end{array}$

[^19]:    

[^20]:    

[^21]:    

[^22]:    

[^23]:    

