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Authors: Jose Carlos Gonzalez-Gomez and Nieves P. Ramirez

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FULL PAPER

Decarboxylative Giese-type reaction of carboxylic acids promoted by visible-light: a sustainable and photoredox neutral protocol.

Nieves P. Ramirez,[a] and Jose C. Gonzalez-Gomez*[a]

Dedication ((optional))

Abstract: This work describes a transition-metal free method for decarboxylative generation of radicals from carboxylic acids and their 1,4-addition to Michael acceptors. The Fukuzumi catalyst ([Acr$^+$-Mes]) enabled this transformation under visible light irradiation, at room temperature and with CO_2 as the only byproduct. Scope and limitations of this protocol were examined using a range of Michael acceptors (15 examples) and a diverse array of carboxylic acids (18 examples). The use of 3-hydroxypivalic acid in this protocol allowed the straighforward formation of a diastereomerically pure δ-lactone. Moreover, when a homoallylic acid was used, a radical cascade took place with the formation of three C-C bonds.

Introduction

The addition of radicals to α,β-unsaturated carbonyl compounds takes place selectively at the β position without any 1,2-addition. This selectivity in the formation of a C-C bond was first discovered by Giese and has found several applications in organic synthesis.[1] The reaction is very efficient when alkyl radicals (high-lying SOMO) are added to electron-deficient olefins (low-lying LUMO), becoming a good alternative to the Michael reaction.[2] This strategy benefits from some issues associated to radical processes, such as: (a) carbonyl, hydroxyl and free amino groups are generally tolerated; (b) since free-radicals are neutral species, they are poorly solvated and tertiary radicals can be used to generate quaternary centers.

Carboxylic acids have gathered much attention as radical sources since they are abundant, non-toxic and renewable feedstocks, which make them ideal starting materials in organic synthesis.[3] Moreover, radicals are produced upon decarboxylation and the elimination of CO_2, as a traceless by-product, does not impact on their reactivity. Decarboxylative radical generation dated back to the classical works of Kolbe, Hunsdiecker and Barton, among others.[4] In the last two decades, the use of transition-metal catalysts has expanded the scope of this strategy, but still high temperatures are required and only scarce examples of C_{sp3}-CO_2H decarboxylation were reported for cross-coupling reactions.[5]

[a] Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain.
E-mail: josecarlos.gonzalez@ua.es.

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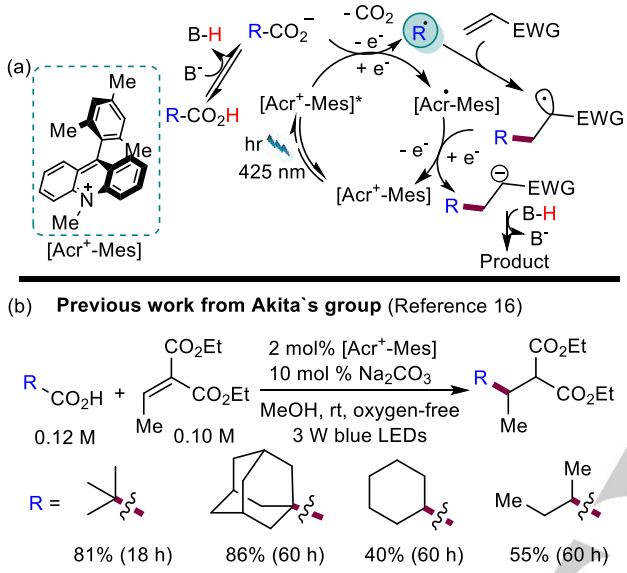
Very recently, visible-light-promoted photoredox catalysis has emerged as a powerful and sustainable tool for the generation of radicals from carboxylic acids at room temperature.[6] Interestingly, if a photoexcited catalyst is oxidant enough to remove an electron from a carboxylate anion [$E(RCOO^{\bullet}/RCOO^{-}) \approx +1.1$ to $+1.5$ V vs SCE],[7] after rapid decarboxylation of aliphatic acyloxy radicals,[8] this radical can be added to electron-poor alkenes and the new α-acyl radical could be reduced [$E(R^{\bullet}/R^{-}) \approx -0.7$ to -0.6 V vs SCE][9] and protonated. In this last step, the 1,4-adduct is delivered, while regenerating the photocatalyst and also the base (Scheme 1a). Since the process is redox-neutral, stoichiometric amounts of chemicals and wastes (except CO_2) are avoided, being a valuable strategy to increase molecular complexity within the principles of "Green-Chemistry".[10] This strategy was first put into practice by Yoshimi's group, using 10 mol % of 1,4-dicyanonaphthalene and phenanthrene as a catalytic system, but still using UV light and very dilute conditions.[11] Almost at the same time, Nishibayashi and coworkers found an iridium photocatalyst $[Ir(ppy)_2bpy]^+$ competent for the visible-light-promoted decarboxylative addition of arylacetic acids to Michael acceptors.[12] Soon after, fine tuning of the iridium photocatalyst structure and reaction conditions allowed to MacMillan's group to find a protocol for this transformation amenable to a wide range of carboxylic acids and electron-deficient olefins.[13] Very recently, iridium-based photocatalysts have also been successful in the decarboxylative Giese-type reaction of α-aminoacids.[14] Given the low abundance of iridium in earth, iridium catalysts are expensive. Consequently, cheaper and more sustainable catalysts are desired for this transformation. In this context, the group of Koike and Akita has reported that organic [Acr-Mes]ClO_4 (Fukuzumi catalyst)[15] is also a competent photocatalyst in this neutral photoredox process. However, only four acids were examined with the same Michael acceptor and the efficiency of the reaction was rather low for secondary acids (Scheme 1b).[16] Encouraged by these results, we decided to reexamine the reaction conditions in order to improve the applicability of this organic photoredox catalyst in the decarboxylative alkylation of carboxylic acids.[17]

Results and Discussion

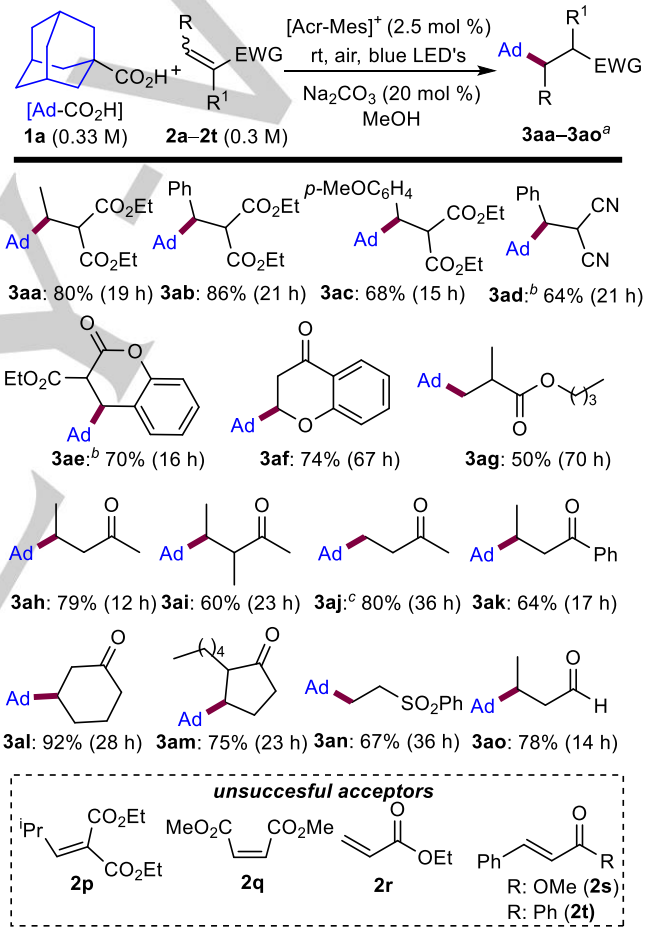
Giving the strong oxidant capacity of the Fukuzumi catalyst,[15] it is not surprising that carboxylic acids, or more efficiently the corresponding carboxylates, can act as reductive quenchers of this photocatalyst. Following the general mechanism for decarboxylative alkylation depicted in Scheme 1a, the turnover of [Acr$^+$-Mes] is proposed to occur by ET from the [Acr$^{\bullet}$-Mes] to the

α-acyl radical. Since the acridinyl radical is a fairly weak reductant [$E_{1/2}$ ($PC^+/PC^•$)= -0.57 V vs SCE],[15] it was not clear at the outset of this work that a range of α-substituted alkyl radicals could efficiently regenerate the photocatalyst. For example, according to the reported reduction potential of $CH_3CH^•–CO_2Me$ ($E_{1/2}$ = -0.66 V vs SCE),[9] the reaction with the acridinyl radical would operate against a moderate potential gradient (about 100 mV). We reasoned that a final fast and thermodynamically favor protonation would compensate this issue for some acceptors.



Scheme 1. (a) Plausible mechanism for a photoredox neutral decarboxylative Giese-type reaction catalyzed by [Acr^+-Mes] and base. (b) Previous work.

With the precedents above mentioned, we decided to screen different Michael acceptors with adamantane-1-carboxylic acid (**1a**). The results of this study are shown in Scheme 2. It is worth mentioning that due to the steric bulkiness of adamantane, radical chemistry is very convenient for its derivatization and this moiety has been quintessential for the development of new drugs and catalysts.[18]. With apparently minor modifications from Akita's conditions (Scheme 1b), we [0.2 equiv of Na_2CO_3, under air atmosphere and using one bulb of 12 x 1 W blue leds and 0.3 M of **2**] were able to isolate compound **3aa** in similar excellent yields but in a significant shorter time (19 h vs 60 h). Importantly, careful deoxygenation and the use of inert atmosphere were not necessary to achieve this goal, simplifying this procedure even more. Under these conditions, other double activated Michael acceptors gave the corresponding products (**3ab**-**3ae**) in very good yields after only 15 to 21 h of irradiation. Notably, 4-chromenone (**2f**) and butyl methacrylate (**2g**) afforded compounds **3af** and **3ag** in good yields, although longer reaction times were necessary. Apparently, the push-pull effect in 4-chromenone and the increased stability of the α-Me-α-acyl radical (or its higher nucleophilicity) with methacrylate acceptor, had a positive impact on the reactivity. We were pleased to find that acyclic (**2h–2k**) and cyclic (**2l**, **2m**) α,β-unsaturated ketones furnished the expected products (**3ah**-**3am**) in very good isolated yields after reasonable reaction times (12 – 36 h). Vinylsulfone **2n** was also a suitable substrate under the reaction conditions to obtain **3an** in good yield and, more importantly, compound **3ao** was obtained in very good yield after only 14 h when crotonaldehyde (**2o**) was used as acceptor. On the contrary, sterically demanding acceptor **2p** failed to add the bulky adamantane moiety. In addition, substrates substituted at α-position by a single ester group (**2q**, **2r** and **2s**) also failed to react, probably because the α-acyl radical is unable to reoxidize [$Acr^•$-Mes]. Moreover, (*E*)-chalcone (**2t**) failed to give any product under the same reaction conditions, likely due to the competitive generation of a stable benzylic radical that is not capable to recycle the catalyst.

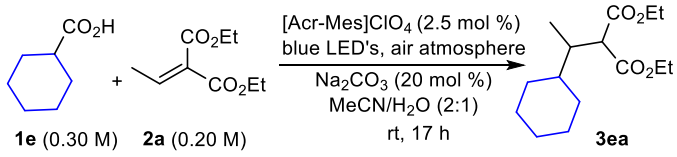


Scheme 2 Scope of electron-deficient alkenes. [a]Isolated pure product. [b]1.7:1 MeOH/EtOAc (0.185 M) was used as solvent mixture to improve the solubility of substrates. [c]3 equiv of volatile MVK were used.

Regarding the carboxylic acid partners, it was reported that the reaction of secondary substrates examined (**1e** and **1f**) under the conditions disclosed by Koike and Akita never went to completion (Scheme 1b).[16] Consequently, we decided to examine this issue in more detail using cyclohexane carboxylic acid (**1e**) and diethyl

2-ethylidene malonate (**2a**) as acceptor in a model reaction. The results of this study are summarized in Table 1.

Table 1. Optimization of reaction conditions.

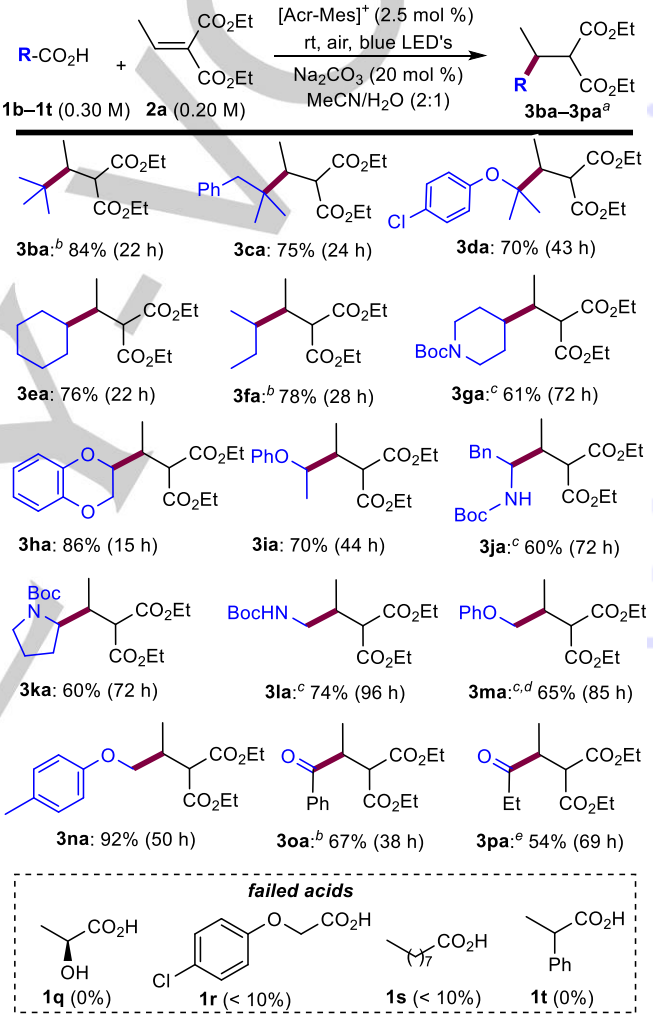


1e (0.30 M) **2a** (0.20 M) **3ea**

Entry	Modification from standard conditions	Yield (%)[a]
1	none	92
2	in MeOH (0.3 M)	77
3	in CF_3CH_2OH (0.3 M)	0
4	in *t*-BuOH (0.3 M)	12
5	in $[CH_2Cl]_2$/MeOH (2:1)	72
6	in Me_2CO/H_2O (2:1)	32
7	in MeCN/H_2O (1:1)	20
8	in MeCN/H_2O (3:1)	50
9	under argon atmosphere	59
10	under oxygen atmosphere (1 atm)	71
11	**1e** (1 equiv) : **2a** (1 equiv)	57
12	**1e** (1 equiv) : **2a** (1.5 equiv)	58
13	blue LED 2 bulbs (12 W)	89
14	white LED bulb (13.5 W)	77
15	Sunlight (10 h)	70[b]
16	CFL light bulb (18 W)	0
17	in the dark	0
18	5 mol % of photocatalyst (10 h)	100
19	1 mol % photocatalyst	25
20	without photocatalyst	0
21	with 20 mol % of Cs_2CO_3	90
22	with 20 mol % of DBU	55
23	without base	23

[a] [a]Yield determined by GC using adamantane as internal standard. [b] See SI for details. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

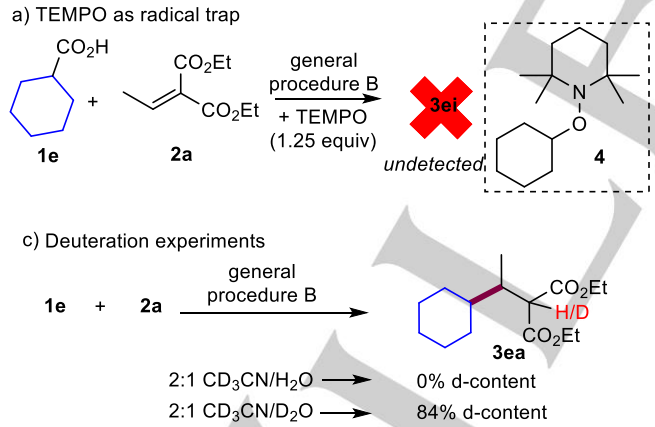
After some experimentation, we have found that the solvent system has a significant impact on the reaction (entries 1-9), obtaining the best results in 2:1 MeCN/H_2O and observing some competitive Michael addition of MeOH when it is used as solvent. To our delight, when the reaction was run under air atmosphere, it was completed after only 17 h (entry 1). Surprisingly, an argon atmosphere (entry 9) had an even more deleterious effect on the yield than an oxygen atmosphere (entry 10).[19] Regarding the stoichiometry, a slight excess of acid (1.5 equiv.) was found beneficial (entries 1, 11 and 12) and it was also helpful to work under concentrated conditions (0.2 − 0.3 M). It was clearly demonstrated that the reaction progress depends highly on the source of light (entries 1, 13-17), obtaining optimal results with intense blue LEDs (12 x 1W). This could also explain the difference in the reaction rate observed under Akita's conditions (3W blue LEDs, Scheme 1b) and ours. Since it has been recently reported that the reductive quenching of [Acr$^+$-Mes]* by carboxylates has low efficiency, we examined the use of two blue LED bulbs, but the yield of the reaction was similar (entry 13 vs 1).[20] Control experiments revealed that the reaction absolutely requires the photocatalyst (entry 20). In addition, while full conversion is achieved after only 10 h using 5 mol % of catalyst (entry 18), similar results are obtained with 2.5 mol % after 17 h and the reaction is significantly slower when the load of photocatalyst is reduced even further (entry 19). It was also found that the reaction progress poorly without base (entry 23). The use of 20 mol % of Cs_2CO_3 leads to similar results than with Na_2CO_3, while lower yields were achieved with DBU (entries 21 and 22).



Scheme 3. Scope of acids. [a]Isolated pure product. [b]2 equivalents of acid **1** were used. [c]Another portion of photocatalyst (2.5 mol %) was added after 48 h. [d] Another portion of acid **1** (1.5 equiv.) was added after 48 h. [e]See SI for details.

Having found these new optimized conditions, we examined the scope of acids with this protocol, using acceptor **2a** (Scheme 3). Tertiary carboxylic acids, including natural clofibric acid (**1d**), participate efficiently in the reaction (products **3ba**-**3da**) to generate quaternary centers. Secondary cyclic and acyclic acids were also suitable substrates with this protocol (**1e**-**1k**). Notably,

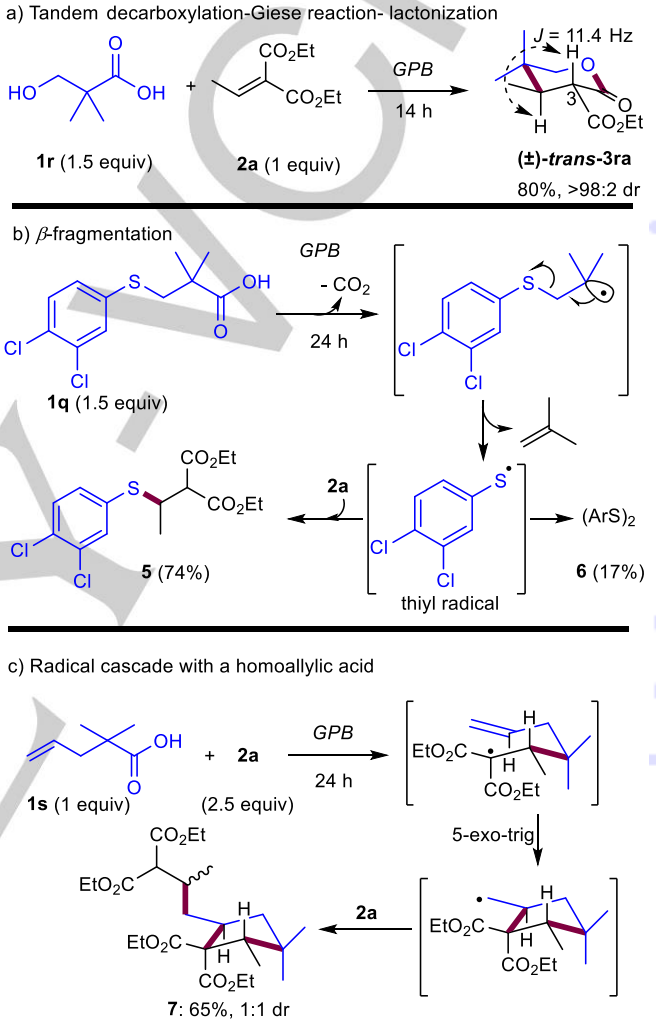
secondary α-oxyacids **1h** and **1i** furnished the corresponding conjugate adducts (**3ha** and **3ia**) in good to excellent yields. Since ethers are formed, this protocol represents a good alternative to the classic Williamson ether synthesis. In addition, natural *N*-Boc protected secondary α-aminoacids provide the corresponding α-alkylamines (**3ja** and **3ka**) in synthetically useful yields. Primary α-amino (from glycine derivative **1l**) and α-oxyacids (from phenoxyacetic derivatives **1m** and **1n**) are also suitable substrates. This procedure allowed the formation of aminomethyl derivative **3la** and aryloximethyl derivative **3ma** and **3na** in good to excellent yields. Importantly, for phenoxyacetic derivatives, electron-donating groups in the aromatic ring accelerate the reaction (**1m** vs **1n**). Remarkably, α-ketoacids were well tolerated, not only aromatic 2-oxophenylacetic acid (**1o**), but also the aliphatic 2-oxoethyl acetic acid (**1p**), gave the corresponding products (**3oa** and **3pa**) in reasonable good yields. This method to build 1,4-dicarbonyl compounds is complementary to the classic Stetter reaction.[21] Very recently, the visible-light mediated decarboxylative 1,4-addition of a range of aromatic α-ketoacids to different Michael acceptors was successfully accomplished using an iridium photocatalyst.[22] Although our protocol furnished compound **3pa** in a moderate yield, we have not found in the literature other examples for the decarboxylative coupling of aliphatic α-ketoacids with Michael acceptors. It is worth mentioning that (*S*)-lactic acid (**1q**) failed in this protocol, most likely due to formation of acetaldehyde after oxidative decarboxylation. Electron-poor phenoxyacetic derivatives (such as **1r**), as well as common primary aliphatic acids (**1s**) and arylacetic acids (e.g. **1t**) failed to provide the conjugate adduct in synthetically useful yields.[23]



Scheme 4. Mechanistic studies

To gain insight into the reaction pathway, we confirmed that the reaction of **1e** and **2a** was completely inhibited in the presence of TEMPO (Scheme 4a) and cyclohexyl radical was trapped to form compound **4** (detected by LC-MS, see SI). Moreover, when the reaction was conducted in CD_3CN/H_2O, incorporation of deuterium was not observed in product **3ea**, excluding the possibility of hydrogen abstraction from the solvent (Scheme 4b).

In contrast, high content of deuterium was observed for the product when D_2O was used as co-solvent. This result is in accordance with a single electron reduction of the α-acyl radical and final deuteration with D_2O and, in a minor extend, protonation with the *in-situ* formed small amount of H_2O to regenerate the base (Scheme 1).



Scheme 5. Synthetic applications.

Some synthetic applications accomplished with the developed protocol are depicted in Scheme 5. When hydroxypivalic acid (**1r**) was used under standard conditions, the free hydroxyl group was well tolerated and after conjugated addition, the lactonization took place smoothly to afford compound **3ra** as a single diastereoisomer (according to ^{1}H- and ^{13}C-NMR). Since poor diastereoselection was observed for other studied examples, we think that this should be the result of a thermodynamic equilibration by deprotonation-protonation at C_3. In addition, when acid **1q** was used in our decarboxylative alkylation protocol with acceptor **2a**, compound **5** was isolated in very good yield, as well

as minor amounts of disulfide **6** (Scheme 5b). Based on the radical nature of this process, we presume that after decarboxylation, β-fragmentation takes place efficiently to release isobutene and the aromatic thiyl radical, which is quickly trapped by acceptor **2a**.[24] Finally, we took advantage of our protocol to develop a radical cascade where two molecules of acceptor **2a** are incorporated in the product and three new σ C-C bonds are formed (Scheme 5c). For this transformation, homoallylic acid **1s** was put into react with acceptor **2a** (2.5 equiv.) under standard conditions, after decarboxylation and radical addition, fast *5-exo-trig* cyclization took place to generate a primary nucleophilic radical that was trapped by another molecule of Michael acceptor. Upon formation of the new electrophilic radical, electron transfer to [Acr•-Mes] could occurs, regenerating the photocatalyst, and final protonation allowed formation of compound **7** in good yield. Remarkably, only two diastereoisomers out of four are formed (GC-MS, ^{1}H, ^{13}C-NMR). It seems reasonable that the diastereocontrol is achieved in the cyclization step, following a chairlike transition state akin to the Beckwith stereoelectronic model.[25]

Conclusions

In conclusion, we have demonstrated the applicability of visible-light induced decarboxylative Giese-type reaction, catalysed by [Acr^{+}-Mes], for a range of substrates. The transformation is redox neutral and the only residue is CO_2. Regarding the acceptor, not only alkylidene malonates/malonitriles were suitable substrates, but also α-substituted acrylates, conjugated ketones/aldehydes and conjugated sulfones. The scope of carboxylic acids includes mainly tertiary and secondary substrates diversely substituted, as well as α-ketoacids and primary α-amino and α-oxy acids. Compare to other existing methods, some salient features of this protocol are: (a) is free of nobel-metal catalysts; (b) only 20 mol % of cheap Na_2CO_3 is used; (c) an aqueous solvent mixture is used and neither deoxygenation nor inert atmosphere is required. We hope that this work contributes to the transformation of carboxylic acids –renewable feedstocks– into pharmaceuticals or fine chemicals using Green Chemistry.

Experimental Section

General Remarks: TLCs were performed on silica gel 60 F_{254}, using aluminium plates and visualized by exposure to ultraviolet light or using different stains (PMA, $KMnO_4$ or Ninhydrin). Flash chromatographies (FC) were carried out on handpacked columns of silica gel 60 (230 – 400 mesh). Infrared (IR) analysis was performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1}. LRMS were performed in a mass spectrometer coupled with a gas chromatographer (GC); the mobile phase was helium (2 mL/min); HP-1 column of 12 m was used; temperature program starts at 80 ºC for 3 min, then up to 270 ºC with a rate of 20 ºC/min, and 17.5 min at 270 ºC. HRMS analyses were carried out using the Electron Impact (EI) mode at 70 eV by Q-TOF. ^{1}H NMR spectra were recorded at 300 or 400 MHz for ^{1}H-NMR and 75 or 100 MHz for ^{13}C-NMR, using $CDCl_3$ as solvent and TMS as an internal standard (0.00 ppm). ^{13}C-NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm.

General procedure A (*GPA*) for the preparation of adamantane derivatives (Scheme 3): In a microwave tube, equipped with a stirring bar, were introduced adamantane-1-carboxylic acid (**1a**, 99 mg, 0.55 mmol, 1.10 equiv.), Na_2CO_3 (4.06 mg, 0.10 mmol, 20 mol %) and [Acr-Mes]ClO_4 (5.2 mg, 2.5 mol %), followed by a solution of the desired Michael acceptor (0.50 mmol) in MeOH (1.7 mL). The yellow solution was irradiated using blue LED's and stirred at room temperature, without any inert atmosphere, until complete conversion was observed (monitored by TLC and/or GC). The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography.

Diethyl 2-(1-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)ethyl)malonate (3aa, Scheme 2):[13] Prepared according to *GPA*, after 19 h. It was purified by FC (Hexane/EtOAc 97:3 to 90:10) and obtained as a colorless oil (128 mg, 0.40 mmol, 80%): TLC R_f 0.12 (Hexane/EtOAc 97:3); IR *v* 2908, 2848, 1756, 1727, 1447, 1147, 1032, 733 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.57 (d, *J* = 5.2 Hz, 1H), 2.08 (dd, *J* = 7.4, 5.5 Hz, 1H), 1.97 (br s, 3H), 1.71 - 1.59 (m, 7H), 1.52 (br s, 5H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5 (C), 169.9 (C), 61.4 (CH_2), 61.0 (CH_2), 52.0 (CH), 43.2 (CH), 39.5 (3 × CH_2), 37.1 (3 × CH_2), 35.3 (C), 28.7 (3 × CH), 14.19 (CH_3), 14.15 (CH_3), 10.5 (CH_3); GC R_T 19.896 min; LRMS (EI) *m/z* (%) =277 (M^{+}-C_2H_5O, 4), 276 (8), 136 (11), 135 (100), 93 (10).

(Diethyl 2 - ((3*r*, 5*r*, 7*r*)-adamantan-1-yl(phenyl)methyl)malonate (3ab, Scheme 2): Prepared according to *GPA*, after 21 h. It was purified by FC (Hexane/EtOAc 99:1 to 85:15) and obtained as a pale yellow oil (166 mg, 0.43 mmol, 86%): TLC R_f 0.19 (Hexane/EtOAc 97:3); IR *v* 2905, 2847, 1752, 1724, 1257, 729, 684 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26 - 7.07 (m, 5H), 4.32 - 4.14 (m, 2H), 4.00 (d, *J* = 10.8 Hz, 1H), 3.77 - 3.61 (m, 2H),3.34 (d, *J* = 10.8 Hz, 1H), 1.91 (br s, 3H), 1.66 - 1.46 (m, 12H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.78 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.7 (C), 168.5 (C), 138.9 (C), 127.3 (2 × CH), 126.6 (3 × CH), 61.8 (CH_2), 61.3 (CH_2), 56.2 (CH), 53.7 (CH) 40.0 (3 × CH_2), 36.8 (3 × CH_2), 36.2 (C), 28.7 (3 × CH), 14.1 (CH_3), 13.5 (CH_3); GC R_T 25.638 min; LRMS (EI) *m/z* (%) = 384 (M^{+}, 2), 136 (11), 135 (100), 93 (6); HRMS (EI) *Calcd.*for $C_{24}H_{32}O_4$ 384.2301, found 384.2302.

Diethyl 2-((3*r*, 5*r*, 7*r*)-adamantan-1-yl(4-methoxyphenyl)methyl)-malonate (3ac, Scheme 2): Prepared according to *GPA*, after 15 h. It was purified by FC (Hexane/EtOAc 95:5 to 85:15) and obtained as a white solid (141 mg, 0.34 mmol, 68%): TLC R_f 0.15 (Hexane/EtOAc 97:3); IR *v* 2971, 2888, 2300, 1767, 1716, 1457, 1309, 1194, 1047, 1033, 761 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 4.31 - 4.13 (m, 2H), 3.96 (d, *J* = 10.7 Hz, 1H), 3.77 (s, 3H), 3.76 - 3.68 (m, 2H), 3.29 (d, *J* = 10.7 Hz, 1H), 1.91 (s, 3H), 1.70 - 1.42 (m, 12H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.8 (C), 168.6 (C), 158.2 (C), 130.9 (C), 112.7 (4 × CH), 61.8 (CH_3), 61.2 (CH_2) 55.4 (CH_2), 55.2 (CH), 53.7 (CH), 40.0 (3 × CH_2), 36.9 (3 × CH_2), 36.3 (C), 28.7 (3 × CH_3), 14.1 (CH_3), 13.7 (CH_3); GC R_T 16.558 min; LRMS (EI) *m/z* (%) = 414 (M^{+}, 18), 279 (16), 278 (18), 255 (13), 136 (11), 135 (100); HRMS (EI) *Calcd.*for $C_{25}H_{34}O_5$ 414.2406, found 414.2414.

2-((3*r*, 5*r*, 7*r*)-adamantan-1-yl(phenyl)methyl)malononitrile (3ad, Scheme 2): Prepared according to *GPA*, after 21 h, but in this case MeOH/EtOAc (1.7 mL/1 mL) was the solvent mixture to improve the solubility of benzylidenemalonitrile. It was purified by FC (Hexane/EtOAc 97:3 to 85:15) and obtained as a white solid (93 mg, 0.32 mmol, 64%): TLC R_f 0.08 (Hexane/EtOAc 97:3); IR *v* 2937, 2900, 1713, 1048, 703 cm^{-1};^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 5H), 4.25 (d, *J* = 5.4 Hz, 1H), 2.80 (d, *J* = 5.4 Hz, 1H), 2.02 (s, 3H), 1.78 - 1.48 (m, 12H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 135.4 (CH), 129.8 (C), 128.68 (2 × CH), 128.6 (2 × CH), 113.6 (C), 113.4 (C), 58.1 (CH), 40.5 (3 × CH_2), 36.6 (C), 36.4 (3 × CH_2), 28.5 (3 × CH_3), 23.9 (CH); GC R_T 22.913 min; LRMS (EI) *m/z* (%) = 290 (M^{+},1),

136 (11), 135 (100), 93 (10); HRMS (EI) *Calcd.*for $C_{20}H_{22}N_2$ 290.1783, found 290.1782.

Ethyl 4-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)-2-oxochroman-3-carboxylate (3ae, Scheme 2): Prepared according to *GPA*, after 16 h, but in this case the solvent mixture was MeOH/EtOAc (1.7 mL/1 mL) to improve the solubility of ethyl 2-oxo-2*H*-chromene-3-carboxylate. It was purified by FC (Hexane/EtOAc 95:5 to 90:10) and obtained as a white solid (124 mg, 0.35 mmol, 70%, >98:2 *dr* according to ^{1}H-NMR): TLC R_f 0.06 (Hexane/EtOAc 97:3); IR *v* 2971, 2888, 2300, 1767, 1716, 1457, 1309, 1194, 1033, 761 cm^{-1};^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 -7.25 (m, 1H), 7.15 - 7.05 (m, 3H), 4.12 - 4.04 (m, 1H), 4.02 (d, *J* = 1.3 Hz, 1H), 4.00 - 3.91 (m, 1H), 2.96 (d, *J*= 0.7 Hz, 1H), 1.98 (br s, 3H), 1.70 - 1.52 (m, 12H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.3 (C), 166.2 (C), 151.8 (C), 131.4 (CH), 129.0 (CH), 124.0 (CH), 120.6 (C), 117.0 (CH), 62.3 (CH_2), 51.7 (CH), 47.2 (CH), 39.5 (3 × CH_2), 36.6 (3 × CH_2), 36.2 (C), 28.4 (3 × CH), 13.9 (CH_3); GC R_T 23.503 min; LRMS (EI) *m/z* (%) = 282 (M^++1-$C_3H_5O_2$, 4), 281 (M^+-$C_3H_5O_2$, 1), 136 (12), 135 (100), 93 (12), 91 (10), 79 (10); HRMS (EI) *Calcd.*for $C_{22}H_{26}O_4$ 354.1831, found 354.1812.

2-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)chroman-4-one (3af, Scheme 2):[26] Prepared according to *GPA*, after 67 h. It was purified by FC (Hexane/EtOAc 97:3 to 95:5) and obtained as a colorless oil (105 mg, 0.37 mmol, 74%): TLC R_f 0.27 (Hexane/EtOAc 97:3); IR *v* 2908, 2859, 1678, 1601, 1461, 1313, 1229, 1038, 752 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.46 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 1H), 7.02 - 6.94 (m, 2H), 3.91 (dd, *J* = 13.6, 3.1 Hz, 1H), 2.67 (qd, *J* = 16.5, 8.3 Hz, 2H), 2.06 (br s, 3H), 1.94 - 1.40 (m, 12H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 193.9 (C), 162.4 (C), 135.9 (CH), 127.0 (CH), 121.0 (C + CH), 118.0 (CH), 85.6 (CH), 37.9 (3 × CH_2), 37.24 (CH_2), 37.17 (3 × CH_2), 36.0 (C), 28.3 (3 × CH); GC R_T 23.746 min; LRMS (EI) *m/z* (%) = 283 (M^++1, 19), 282 (M^+, 94), 281 (M^+-1, 15), 147 (50), 136 (11), 135 (100), 121 (12), 120 (10), 93 (14), 92 (10), 91 (12), 79 (12).

Butyl 3-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)-2-methylpropanoate (3ag, Scheme 2): Prepared according to *GPA*, after 70 h. It was purified by FC (Hexane/EtOAc 97:3 to 95:5)and obtained as a colorless oil (68 mg, 0.25 mmol, 50%): TLC R_f 0.43 (Hexane/EtOAc 97:3); IR *v* 2957, 2898, 2846, 1727, 1451, 1181, 1121, 1095 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.12 - 3.98 (m, 2H), 2.54 (dqd, *J* = 14.1, 7.1, 3.1 Hz, 1H), 1.92 (brs, 3H), 1.79 - 1.55 (m, 9H), 1.54 - 1.33 (m, 8H), 1.13 (d, *J* = 7.1 Hz, 3H), 1.01 (dd, *J* = 14.2, 3.1 Hz, 1H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.3 (C), 64.2 (CH_2), 48.7 (CH_2), 42.4 (3 × CH_2), 37.1 (3 × CH_2), 34.5 (CH), 32.8 (C), 30.8 (CH_2), 28.8 (3 × CH), 20.7 (CH_2), 19.3 (CH_3), 13.9 (CH_3); GC R_T 17.869 min; LRMS (EI) *m/z* (%) = 278 (M^+, 5), 143 (12), 136 (12), 135 (100); HRMS (EI) *Calcd.*for $C_{18}H_{30}O_2$ - C_4H_9O 204.1514, found 204.1517.

4-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)pentan-2-one (3ah, Scheme 2): Prepared according to *GPA*, after 12 h, but in this case the reaction was performed using 1-adamantanecarboxylic acid (90 mg, 0.50 mmol) and 3-penten-2-one (103 µL, 0.75 mmol, 1.5 equiv.). It was purified by FC (Hexane/EtOAc 95:5) and obtained as a colorless oil (88 mg, 0.40 mmol, 79%): TLC R_f 0.38 (Hexane/EtOAc 97:3); IR *v* 1707, 1255, 723, 703 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.59 (dd, *J* = 15.7, 2.6 Hz, 1H), 2.14 (s, 3H), 2.06 (dd, *J* = 15.7, 10.3 Hz, 3H), 1.97 (br s, 3H), 1.74 - 1.57 (m, 6H), 1.48 (s, 5H), 0.79 (d, *J* = 6.9 Hz, 3H);^{13}C-NMR (101 MHz, $CDCl_3$) δ 210.2 (C), 45.5 (CH_2), 39.4 (3 x CH_2), 39.0 (CH_3), 37.4 (3 x CH_2), 34.4 (C), 30.5 (CH), 28.8 (3 x CH), 13.7 (CH_3); GC R_T 16.080 min; LRMS (EI) *m/z* (%) = 220 (M^+, 1), 202 (15), 136 (11), 135 (100), 93 (14), 79 (14); HRMS (EI) *Calcd.*for $C_{15}H_{24}O$ 220.1827, found 220.1836.

4-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)-3-methylpentan-2-one (3ai, Scheme 2): Prepared according to *GPA*, after 23 h. It was purified by FC (Hexane/EtOAc 97:3 to 90:10) and obtained as a pale yellow oil (70.2 mg, 0.30 mmoles, 60%, >98:2 *dr* according to NMR and GC experiments): TLC R_f 0.22 (Hexane/EtOAc 97:3); IR *v* 2908, 2849, 1702, 1442, 1342, 1087, 1048, 871 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.18 (qd, *J* = 7.1, 3.4 Hz, 1H), 2.17 (s, 3 H), 1.97 (br s, 3H), 1.73 - 1.47 (m , 12H), 1.32 - 1.23 (m, 1H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 7.4 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 213.9 (C), 48.7 (CH), 46.3 (CH), 40.3 (3 × CH_2), 37.3 (3 × CH_2), 36.1 (C), 30.1 (CH_3), 28.8 (3 × CH), 18.3 (CH_3), 10.4 (CH_3); GC R_T 16.223 min; LRMS (EI) *m/z* (%) = 216 (M^+ - H_2O, 11), 136 (11), 135 (100), 93 (10), 79 (10); HRMS (EI) *Calcd.*for $C_{16}H_{26}O$ 234.1984, found 234.1983.

4-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)butan-2-one (3aj, Scheme 2):[27] Prepared according to *GPA*, after 36 h, but in this case the reaction was performed using 1-adamantanecarboxylic acid (90 mg,0.50 mmol) and methyl vinyl ketone (125 µl, 1.5 mmol, 3 equiv.). It was purified by FC (Hexane/EtOAc 97:3 to 90:10) and obtained as a colorless oil (83 mg, 0.40 mmol, 80%): TLC R_f 0.24 (Hexane/EtOAc 97:3); IR *v* 2902, 2844, 1713, 1269, 737, 700 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.44 - 2.31 (m, 2H), 2.15 (s, 3H), 1.95 (br s, 3H), 1.76 - 1.54 (m, 6H), 1.46 - 1.45 (m, 6H), 1.40 - 1.30 (m, 2H); ^{13}C -NMR (101 MHz, $CDCl_3$) δ 210.2 (C), 42.3 (3 x CH_2), 37.9 (CH_2), 37.6 (CH_2), 37.2 (3 x CH_2), 31.9 (C), 30.0 (CH_3), 28.8 (3 x CH); GC R_T 15.479 min; LRMS (EI) *m/z* (%) = 206 (M^+, 1), 189 (5), 188 (33), 136 (11), 135 (100), 93 (13), 79 (13).

3-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)-1-phenylbutan-1-one (3ak, Scheme 2): Prepared according to *GPA*, after 17 h. It was purified by FC (Hexane/EtOAc 97:3 to 85:15) and obtained as a pale yellow oil (90 mg, 0.32 mmol, 64%): TLC R_f 0.44 (Hexane/EtOAc 97:3); IR *v* 2898, 2849, 1678, 1442, 1205, 999, 743, 674 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 - 7.88 (m, 2H), 1H), 7.58 - 7.51 (m, 1H), 7.50 - 7.41 (m, 2H), 3.16 (dd, *J* = 15.4, 2.9 Hz, 1H), 2.57 (dd, *J* = 15.4, 10.4 Hz, 1H), 2.00 (br s, 3H), 1.89 - 1.78 (m, 1H), 1.76 - 1.59 (m, 6H), 1.57 - 1.56 (m, 6H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 201.7 (C), 137.6 (C), 132.9 (CH), 128.6 (2 x CH), 128.3 (2 x CH), 40.2 (CH_2), 39.6 (3 x CH_2), 37.4 (3 x CH_2) , 34.8 (C + CH), 28.8 (3 x CH), 13.7 (CH_3); GC R_T 22.617 min; LRMS (EI) *m/z* (%) = 282 (M^+, 10), 162 (18), 147 (22), 146 (13), 136 (11), 135 (100), 105 (19), 93 (11), 79 (11), 77 (17); HRMS (EI) *Calcd.* for $C_{20}H_{26}O$ 282.1984, found 282.1999.

3-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)cyclohexanone (3al, Scheme 2):[28] Prepared according to *GPA*, after 28 h. It was purified by FC (Hexane/EtOAc 97:3 to 90:10) and obtained as a pale yellow oil (108 mg, 0.46 mmol, 92%): TLC R_f 0.31 (Hexane/EtOAc 97:3); IR *v* 2898, 2848, 1701, 1451, 1231, 1058 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.50 - 2.03 (m, 5H), 1.98 (br s, 4H), 1.74 - 1.59 (m, 6H), 1.52 - 1.51 (m, 6H), 1.41 - 1.19 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 213.5 (C), 49.8 (CH), 42.2 (CH_2), 41.6 (CH_2), 39.5 (3 × CH_2), 37.3 (3 × CH_2), 34.5 (C), 28.7 (3 × CH_3), 25.8 (CH_2), 24.7 (CH_2); GC R_T 19.014 min; LRMS (EI) *m/z* (%) = 232 (M^+, 4), 136 (11), 135 (100), 93 (10), 79 (10).

3-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)-2-pentylcyclopentan-1-one (3am, Scheme 2): Prepared according to *GPA*, after 23 h. It was purified by FC (Hexane/EtOAc 98:2 to 95:5) and obtained as a pale-yellow oil (108 mg, 0.375 mmol, 75%, 95:5 *dr* according GC): TLC R_f 0.32 (Hexane/EtOAc 97:3); IR *v* 2900, 2846, 1734, 1451, 1168, 753 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *mixture of diastereoisomers* δ 2.48 - 2.04 (m, 3H), 1.98 (brs, 3H), 1.94 - 1.85 (m, 1H), 1.84 - 1.57 (m, 9H), 1.54 - 1.53 (m, 7H), 1.38 - 1.20 (m, 7H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *mixture of diastereoisomers* δ 223.0 (C=O), 220.6 (C=O), 52.8, 51.4, 51.2, 48.6, 41.6, 40.2, 38.2, 37.3, 36.8, 34.9, 34.6, 32.2, 28.8, 28.6, 27.0, 26.3, 26.2, 22.7 , 22.6, 20.6, 19.8, 14.2; GC R_T 24.300 min and 24.515 min (*two diastereoisomers*); LRMS (EI) *m/z* (%) (*Diastereoisomer A*) = 218 (M^+-C_5H_{11}, 31), 136 (11), 135 (100), 93 (16), 83 (28), 82 (98), 79 (16); *m/z* (%) (*Diastereoisomer B*) = 218 (M^+ - C_5H_{11}, 18), 136 (11), 135 (100), 93 (12),

83 (16), 82 (63), 79 (13); HRMS (EI) *Calcd.* for $C_{20}H_{32}O$ - C_5H_{10} 218.1671, found 218.1678.

(3*r*, 5*r*, 7*r*)-1-(2-(phenylsulfonyl)ethyl)adamantane (3an, Scheme 2):[29] Prepared according to *GPA*, after 36 h. It was purified by FC (Hexane/EtOAc 95:5 to 80:20) and obtained as a white solid (102 mg, 0.335 mmol, 67%): TLC R_f 0.10 (Hexane/EtOAc 97:3); IR *v* 1734, 1373, 1237, 1046, 914, 730 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 - 7.96 (m, 2H), 7.70 - 7.63 (m, 1H), 7.61 - 7.54 (m, 2H), 3.06 (d, *J* = 17.3 Hz, 1H), 3.06 (dd, *J* = 5.1, 3.8 Hz, 1H), 1.94 (br s, 3H), 1.75 - 1.53 (m, 6H), 1.52 - 1.43 (m, 2H), 1.41 - 1.40 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.3 (C), 133.7 (CH), 129.3 (2 × CH), 128.1 (2 × CH), 51.4 (CH_2), 42.0 (3 × CH_2), 36.9 (3 × CH_2), 36.0 (CH_2), 31.9 (C), 28.5 (3 × CH); GC R_T 23.559 min; LRMS (EI) *m/z* (%) = 136 (M^++ 1 - $C_8H_8O_2S$, 11), 135 (100).

3-((3*r*, 5*r*, 7*r*)-adamantan-1-yl)butanal (3ao, Scheme 2: Prepared according to *GPA*, after 14 h. It was purified by FC (Hexane/EtOAc 97:3 to 90:10) and obtained as a colorless oil (80.340 mg, 0.39 mmol, 78%): TLC R_f 0.32 (Hexane/EtOAc 97:3); IR *v* 2924, 2848, 1723, 1707, 1309, 1208, 967, 733 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.71 (dd, *J* = 3.4, 1.3 Hz, 1H), 2.56 (dd, *J* = 16.2, 3.3 Hz, 1H), 2.09 - 1.99 (m, 1H), 1.99 - 1.90 (m, 4H), 1.72 - 1.75 (m, 6H), 1.46 (s, 6H), 0.83 (dd, *J* = 6.9, 0.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 203.9 (C=O), 45.6 (CH_2), 39.4 (3 × CH_2), 37.8 (CH), 37.2 (3 × CH_2), 34.4 (C), 28.7 (3 × CH), 14.0 (CH_3); GC R_T 15.605 min; LRMS (EI) *m/z* (%) = 206 (M^+, 1), 136 (11), 135 (100), 93 (11), 79 (11); HRMS (EI) *Calcd.* for $C_{14}H_{22}O$ 206.1671, found 206.1674.

General procedure B (*GPB*) for the decarboxylative addition of different carboxylic acids to Michael acceptor 2a (Scheme 3): The method is similar to GPA, but in this case a solution of the desired carboxylic acid (0.75 mmol, 1.5 equiv.) and diethyl 2-ethylidene malonate (**2a**, 92 µL, 0.50 mmol) in MeCN (1.7 mL) were charged in the microwave tube, followed by H_2O (0.85 mL).

Diethyl 2-((3, 3-dimethylbutan-2-yl)malonate (3ba, Scheme 3):[16] Prepared according to *GPB*, after 22 h, but in this case 2 equiv. of pivalic acid were used (**1b**, 103 mg, 1mmol). It was purified by FC (Hexane/EtOAc 97:3 to 85:15) and obtained as a pale yellow oil (103 mg, 0.42 mmol, 84%): TLC R_f 0.27 (Hexane/EtOAc 97:3); IR *v* 2962, 1757, 1731, 1466, 1370, 1289, 1147, 1024 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.52 (d, *J* = 5.4 Hz, 1H), 2.30 - 2.19 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H), 0.90 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.3 (C), 169.7 (C), 61.4 (CH_2), 61.0 (CH_2), 53.5 (CH), 42.7 (CH), 33.7 (C), 27.6 (3 × CH_3), 14.14 (CH_3), 14.12 (CH_3) 12.2 (CH_3); GC R_T 13.178 min; LRMS (EI) *m/z* (%) = 229 (M^+ - CH_3, 16), 199 (41), 189 (21), 188 (39), 173 (10), 160 (15), 155 (44), 143 (24), 142 (89), 147 (10), 127 (10), 116 (10), 115 (100), 114 (15), 109 (10), 99 (18), 87 (29), 86 (14), 85 (16), 69 (23), 57 (20), 55 (10).

Diethyl 2-(3, 3-dimethyl-4-phenylbutan-2-yl)malonate (3ca, Scheme 4): Prepared according to *GPB*, after 24 h. It was purified by FC (Hexane/EtOAc100% Hexane to 97: 3 Hexane) and obtained as a colorless oil (120 mg, 0.375 mmol, 75%): TLC R_f 0.22 (Hexane/EtOAc 97:3); IR *v* 2977, 1754, 1725, 1463, 1289, 1148, 697 cm^{-1};^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 - 7.17 (m, 3H), 7.13 - 7.10 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.65 (d, *J* = 4.9 Hz, 1H), 2.56 (d, *J* = 1.6 Hz, 2H), 2.38 (qd, *J* = 7.2 Hz, 4.9 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 7.2 Hz, 3H), 0.83 (s, 3H), 0.82 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.2 (C), 169.7 (C), 138.8 (C), 130.9 (2 × CH), 127.8 (2 × CH), 126.1 (CH), 61.6 (CH_2), 61.2 (CH_2), 53.1 (CH), 45.7 (CH_2), 42.0 (CH), 37.5 (C), 24.5 (CH_3), 24.1 (CH_3), 14.20 (CH_3), 14.15 (CH_3), 12.04 (CH_3); GC R_T 19.440 min; LRMS (EI) *m/z* (%) = 275 (M^+ - C_2H_5, 9), 230 (19), 229 (100), 201 (12), 187 (73), 156 (15), 155 (100), 145 (11), 137 (39), 127 (25), 117 (11), 115 (17), 109 (30), 105 (11), 91 (68), 69 (12); HRMS (EI) *Calcd.* for $C_{19}H_{28}O_4$ 319.1908, found 319.1909.

Diethyl 2-(3-(4-chlorophenoxy)-3-methylbutan-2-yl)malonate (3da, Scheme 3): Prepared according to *GPB*, after 43 h. It was purified by FC (Hexane/EtOAc 97:3 to 95:5) and obtained as a colorless oil (107 mg, 0.3 mmol, 60%): TLC R_f 0.29 (9:1 Hexane/EtOAc); IR *v* 2986, 1724, 1482, 1375, 1234, 1145, 1094, 1036, 850 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.14 (m, 2H), 6.98 - 6.84 (m, 2H), 4.24 - 4.16 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.78 (d, *J* = 6.8 Hz, 1H), 2.77 (p, *J* = 7.1 Hz 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 3H), 1.12 (d, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 169.6 (C), 169.3 (C), 153.3 (C), 129.0 (C + 2 × CH), 125.7 (2 × CH), 83.0 (C), 61.4 (CH_2), 61.2 (CH_2), 53.6 (CH), 43.7 (CH), 25.7 (CH_3), 21.9 (CH_3), 14.19 (CH_3), 14.12 (CH_3), 13.2 (CH_3); GC R_T 20.674 min; LRMS (EI) *m/z* (%) = 229 (M^+ - C_6H_4ClO, 27), 156 (12), 155 (100), 137 (29), 136 (24), 130 (24), 128 (81), 127 (31), 111 (17), 109 (39), 108 (17), 81 (14), 69 (24), 65 (25); HRMS (EI) *Calcd.* for $C_{18}H_{25}ClO_5$ - C_6H_4ClO 229.1440, found 229.1447.

Diethyl 2-(1-cyclohexylethyl)malonate (3ea, Scheme 3):[16] Prepared according to *GPB*, after 22 h. It was purified by FC (97:3 to 85:15 Hexane/EtOAc) and obtained as a pale yellow oil (97 mg, 0.38 mmol, 76%): TLC R_f 0.16 (Hexane/EtOAc 97:3), stained with $KMnO_4$; IR *v* 2977, 2926, 2848, 1730, 1451, 1147, 1032 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.25 - 4.14 (m, 4H), 3.39 (d, *J* = 9.2 Hz, 1H), 2.18 (dqd, *J* = 13.8, 6.9, 4.4 Hz, 1H), 1.82 - 1.49 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 6H), 1.20 – 0.93 (m, 5H), 0.90 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.4 (C), 169.2 (C), 61.3 (CH_2), 61.2 (CH_2), 55.9 (CH), 40.4 (CH), 38.7 (CH), 31.6 (CH_2), 27.5 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 14.2 (2 × CH_3), 13.0 (CH_3); GC R_T 15.943 min; LRMS (EI) *m/z* (%) = 225 (M^+ - C_2H_5O, 13), 187 (48), 161 (91), 160 (100), 141 (26), 133 (39), 132 (11), 115 (39), 114 (10), 110 (10), 109 (19), 90 (10), 87 (18), 81 (16), 69 (24), 67 (11), 55 (16).

Diethyl 2-(3-methylpentan-2-yl)malonate (3fa, Scheme 3):[16] Prepared according to *GPB*, after 28 h, but using 2 equiv. of volatile (±)-2-methylbutyric acid (111 µL, 1 mmol). It was purified by FC (Hexane/EtOAc 95:5 to 85:15) and obtained as a pale yellow oil (95 mg, 0.39 mmol, 78%, 51:49 *dr* according to ^{1}H-NMR): TLC R_f 0.35 (Hexane/EtOAc 97:3), stained with $KMnO_4$; IR *v* 2972, 2939, 2880, 1747, 1725, 1463, 1035, 912, 735 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 5H), 3.39 (d, *J* = 9.4 Hz, 0.48H), 3.31 (d, *J* = 10.4 Hz, 0.46H), 2.44 - 2.31 (m, 0.47H), 2.25 (dqd, *J* = 13.8, 7.0, 4.0 Hz, 0.52H), 1.53 - 1.31 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.95 - 0.86 (m, 6H), 0.82 (d, *J* = 6.9 Hz, 1.46Hz), 0.79 (d, *J* = 6.7 Hz, 1.44H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 169.3 (C), 169.11 (C), 169.09 (C), 169.0 (C), 61.2 (CH_2), 61.1 (CH_2), 56.9 (CH), 56.1 (CH), 38.8 (CH), 36.9 (CH), 36.5 (CH), 36.2 (CH), 28.1 (CH_2), 23.8 (CH_3), 17.5 (CH_3), 14.2 (3 x CH_3), 13.4 (CH_3), 12.5 (CH_3), 12.1 (CH_3), 13.0 (CH_3), 11.2 (CH_3); GC R_T 13.429 min; LRMS (EI) *m/z* (%) = 199 (M^+- C_2H_5O, 19), 187 (11), 161 (30), 160 (100), 141 (18), 133 (37), 132 (11), 115 (39), 114 (13), 88 (12), 87 (20), 86 (12), 69 (23).

Diethyl 2-(1-(1-*tert*-butyl)piperidin-4-yl)ethyl)malonate (3ga, Scheme 3):[16] Prepared according to *GPB*, after 72 h, but in this case another portion of photocatalyst (5.2 mg, 2.5 mol %) was added after 48 h of reaction. It was purified by FC (Hexane/EtOAc 97:3 to 85:15) and obtained as a colorless oil (113 mg, 0.305 mmol, 61%): TLC R_f 0.10 (Hexane/EtOAc 97:3); IR *v* 1746, 1720, 1681, 1426, 1364, 1263, 732, 701 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *mixture of rotamers* δ 4.21 (q, *J* = 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.39 (d, *J* = 8.6 Hz, 1H), 2.65 - 2.52 (m, 2H), 2.30 - 2.14 (m, 1H), 1.67 - 1.46 (m, 2.42H), 1.45 (s, 9.82H), 1.37 - 1.30 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 7H), 1.22 - 1.01 (m, 2H), 0.93 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *mixture of rotamers* δ 169.2 (C), 168.8 (C), 154.9 (C), 79.5 (C), 61.4 (CH_2), 61.3 (CH_2), 55.5 (CH), 44.3 (CH_2), 44.0 (CH_2), 38.9 (CH), 37.9 (CH), 30.4 (CH_2) 28.6 (3 × CH_3), 27.1 (CH_2) 14.2 (2 × CH_3),

13.1 (CH_3); LRMS (DIP) *m/z* (%) = 314 (M^+-C_4H_9, 11), 298 (12), 270 (31), 226 (22), 198 (39), 188 (10), 187 (100), 180 (11), 160 (15), 156 (28), 153 (11), 141 (23), 112 (18), 85 (13), 84 (10), 82 (13), 57 (72), 41 (12).

Diethyl 2-(1-(2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)ethyl)malonate (3ha, Scheme 3): Prepared according to *GPB* after 15 h. It was purified by FC (Hexane/EtOAc 95:5 to 85:15) and obtained as a pale yellow oil (139 mg, 0.43 mmol, 86%, 54:46 *dr* according to ^{1}H-NMR): TLC R_f 0.17 (Hexane/EtOAc); IR *v* 2986, 1737, 1594, 1491, 1262, 1175, 743 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *mixture of diastereoisomers* δ 6.89 - 6.79 (m, 4H), 4.31 (dd, *J* = 11.3, 2.1 Hz, 0.55H), 4.27 - 4.13 (m, 6H), 4.08 - 3.93 (m, 1H), 3.84 (d, *J* = 5.3 Hz, 0.53H), 3.67 (d, *J* = 8.9 Hz, 0.46H), 2.74 - 2.50 (m, 1H), 1.35 - 1.19 (m, 6H), 1.15 (d, *J* = 7.0 Hz, 1.65H), 1.15 (d, *J* = 7.0 Hz, 1.49H); ^{13}C-NMR (75 MHz, $CDCl_3$) *mixture of diastereoisomers* δ 169.0 (C), 168.5 (C), 168.4 (C), 168.3 (C), 143.7 (C), 143.4 (C), 143.3 (C), 143.0 (C), 121.6 (CH), 121.5 (2 × CH), 121.4 (CH), 117.3 (CH), 117.14 (2 × CH), 117.07 (CH), 74.6 (CH), 73.7 (CH), 66.4 (CH_2), 66.2 (CH_2), 61.7 (CH_2), 61.6 (CH_2), 61.5 (CH_2), 61.3 (CH_2), 54.5 (CH), 52.2 (CH), 34.6 (CH), 34.4 (CH), 14.21 (CH_3), 14.18 (CH_3), 14.16 (CH_3), 14.12 (CH_3), 13.1 (CH_3), 11.9 (CH_3); GC R_T 19.393 and 19.460 min (*two diastereoisomers*); LRMS (EI) *m/z (Diastereoisomer A)* (%) = 322 (M^+, 34), 277 (17), 231 (15), 163 (15), 162 (100), 161 (12), 149 (18), 139 (12), 135 (43), 121 (23); *m/z (Diastereoisomer B)* (%) = 322 (M^+, 32), 277 (18), 231 (10), 163 (15), 162 (100), 161 (15), 149 (18), 139 (15), 135 (45), 121 (26); HRMS (EI): *Calcd.*for $C_{17}H_{22}O_6$ – $C_7H_{11}O_4$ 163.0759, found 163.0761.

Diethyl 2-(3-phenoxybutan-2-yl)malonate (3ia, Scheme 3): Prepared according to *GPB*, after 44 h. It was purified by FC (Hexane/EtOAc 95:5) and obtained as a colorless oil (108 mg, 0.35 mmol, 70%, 62:38 *dr* according to ^{1}H-NMR): TLC R_f 0.14 (Hexane/EtOAc 97:3); IR *v* 1717, 1599, 1494, 1265, 1232, 1027, 732, 727, 692 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *mixture of diastereoisomers* δ 7.33 - 7.15 (m, 2H), 6.98 - 6.80 (m, 3H), 4.51 (qd, *J* = 6.3, 3.0 Hz, 0.35H), 4.40 (dq, *J* = 12.3, 6.1 Hz, 0.59H), 4.33 - 3.99 (m, 4H), 3.69 (d, *J* = 6.5 Hz, 0.51H), 3.54 (d, *J* = 9.2 Hz, 0.31H), 2.69 - 2.58 (m, 0.56H), 2.5 - 2.39 (m, 0.40H), 1.33 - 1.05 (m, 12H); ^{13}C-NMR (75 MHz, $CDCl_3$) *mixture of diastereoisomers* δ 169.3 (C), 169.00 (C), 168.96 (C), 168.7 (C), 158.1 (C), 157.7 (C), 129.6 (2 × CH), 121.0 (CH), 120.8 (CH), 116.2 (CH), 115.9 (CH), 75.0 (CH), 73.8 (CH), 61.4 (CH_2), 61.2 (CH_2), 55.2 (CH), 53.7 (CH), 38.82 (CH), 38.78 (CH), 17.0 (CH_3), 16.9 (CH_3), 14.2 (2 ×CH_3), 14.1 (CH_3), 13.9 (CH_3), 12.9 (CH_3), 11.6 (CH_3); GC R_T 17.695 and 17.796 min (*two diastereoisomers*); LRMS (EI) *m/z (Diastereoisomer A)* (%) =216 (M^+ + 1 - C_6H_5O, 11), 215 (88), 187 (11), 169 (24), 141 (100), 123 (24), 121 (16), 113 (49), 97 (22), 95 (16), 94 (31), 77 (20), 69 (10); *m/z (Diastereoisomer B)* (%) = 216 (M^++1 - C_6H_5O, 11), 215 (90), 187 (6), 169 (21), 141 (100), 123 (23), 121 (13) 113 (49), 97 (17), 95 (14), 94 (27), 77 (18), 69 (10); HRMS (EI) *Calcd.* for $C_{17}H_{24}O_5$ 308.1624, found 308.1624.

Diethyl 2-(3-(*tert*-butylamino)-4-phenylbutan-2-yl)malonate (3ja, Scheme 3):[13] Prepared according to *GPB*, after 72 h, but in this case another portion of photocatalyst (5.2 mg, 2.5 mol %) was added after 48 hours of reaction. It was purified by FC (Hexane/EtOAc 95:5 to 70:30) and obtained as a pale yellow oil (122.3 mg, 0.30 mmol, 60%, 57:43 *dr* according to ^{1}H-NMR): TLC R_f 0.10 (Hexane/EtOAc 97:3); IR *v* 2975, 1708, 1502, 1239, 1167, 1028, 702 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *mixture of diastereoisomers and rotamers* δ 7.36 - 7.12 (m, 5H), 4.52 (d, *J* = 9.7 Hz, 0.52H), 4.40 (d, *J* = 10.1 Hz, 0.55H), 4.25 - 4.13 (m, 4H), 3.93 - 3.72 (m, 0.44H), 3.51 (d, *J* = 6.8 Hz, 0.43H), 3.35 (d, *J* = 9.9 Hz, 0.41H), 2.97 (dd, *J* = 13.9, 4.7 Hz, 0.44H), 2.77 (d, *J* = 6.7 Hz, 0.71H), 2.69 - 2.57 (m, 0.49H), 2.52 - 2.37 (m, 0.96H), 1.55 - 1.19 (m, 16H), 1.14 (d, *J* = 6.9 Hz, 1.87 H), 0.95 (d, *J* = 7.0 Hz, 1.41H); ^{13}C-NMR (75 MHz, $CDCl_3$) *mixture of diastereoisomers and rotamers* δ 169.6 (C), 169.0 (C), 168.4 (C), 155.6 (C), 155.4 (C), 138.04 (C), 137.99 (C), 129.4 (CH), 129.2 (CH), 128.49 (CH), 128.47 (CH), 126.5 (CH), 79.3 (C), 79.1 (C), 61.6 (CH_2), 61.4 (CH_2), 55.7 (CH), 55.3 (CH), 54.3 (CH), 52.8 (CH), 39.9 (CH_2), 39.1 (CH_2), 37.2 (CH), 35.8 (CH), 28.3 (CH_3), 28.1 (CH_3), 15.1 (CH_3), 14.2 (CH_3), 14.1 (CH_3), 11.2 (CH_3); LRMS (DIP) *m/z* (%) = 316 (M^+-C_7H_7, 23), 262 (15), 260 (17), 217 (12), 216 (100), 170 (18), 142 (21), 131 (12), 124 (25), 120 (17), 91 (21), 57 (45).

Diethyl 2-(1-(1-*tert*-butoxycarbonyl)pyrrolidin-2-yl)ethyl)malonate (3ka, Scheme 3):[13] Prepared according to *GPB*, after 72 h. It was purified by FC (Hexane/EtOAc97:3 to 85:15) and obtained as a pale yellow oil (107 mg, 0.3 mmol, 60%, 82:18 *dr* according to ^{1}H-NMR):TLC R_f 0.10 (Hexane/EtOAc); IR *v* 1726, 1678, 1382, 1264, 1166, 723, 704 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *mixture of diastereoisomers and rotamers* δ 4.26 - 4.10 (m, 4H), 4.01 - 3.23 (m, 3H), 3.25 - 2.99 (m, 1H), 2.81 - 2.66 (m, 0.76H), 2.62 - 2.50 (m, 0.17H), 2.09 - 1.61 (m, 4H), 1.47 (s, 9H), 1.31 - 1.22 (m, 6H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) *mixture of diastereoisomers and rotamers* δ 169.0 (C), 168.9 (C), 168.8 (C), 155.6 (C), 155.4 (C), 155.3 (C), 80.0 (C), 79.9 (C), 61.4 (CH_2), 61.3 (CH_2), 60.7 (CH), 60.4 (CH), 55.7 (CH), 54.9 (CH), 54.2 (CH), 48.1 (CH_2), 47.7 (CH_2), 47.3 (CH_2), 47.0 (CH_2), 37.2 (CH), 37.0 (CH), 28.6 (CH_3), 28.58 (CH_3), 28.3 (CH_3), 24.3 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 14.22 (CH_3), 14.16 (CH_3), 13.6 (CH_3); LRMS (DIP) *m/z* (%) = 256 (M^+ - C_4H_9, 10), 212 (26), 197 (16), 170 (18), 142 (11), 141 (19), 115 (17), 114 (100), 70 (89), 57 (47), 41 (12).

Diethyl 2-(1-((*tert*-butoxycarbonyl)amino)propan-2-yl)malonate (3la, Scheme 3):[13] Prepared according to *GPB*, after 96 h, but in this case another portion of photocatalyst (2.5 mol %, 5.2 mg) was added after 48 h of reaction. It was purified by FC (Hexane/EtOAc 95:5 to 75:25) and obtained as a pale yellow oil (117 mg, 0.37 mmol, 74%): TLC R_f 0.10 (Hexane/EtOAc); IR *v* 2981, 1718, 1518, 1243, 1167, 1039, 784 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *mixture of rotamers* δ 4.74 (br s, 0.59H), 4.39 - 4.27 (m, 0.68H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.58 - 3.38 (m, 0.36H), 3.31 (d, *J* = 7.4 Hz, 1H), 3.19 - 3.17 (m, 1.78H), 2.45 (p, *J* = 6.8 Hz, 1H), 1.43 (s, 9H), 1.27 (t, *J* = 7.1Hz, 6H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *mixture of rotamers* δ 168.9 (C), 168.7 (C), 156.1 (C), 79.4 (C), 61.54 (CH_2), 61.48 (CH_2), 55.2 (CH), 44.4 (CH), 34.2 (CH_2), 28.54 (CH_3), 28.45 (CH_3), 28.4 (CH_3), 28.1 (CH_3), 15.7 (CH_3), 14.22 (CH_3), 14.20 (CH_3); LRMS (DIP) *m/z* (%) 244 (M^+ - C_2H_5O, 14), 216 (40), 198 (15), 172 (20), 161 (23), 160 (32), 142 (29), 126 (19), 115 (29), 101 (26), 87 (15), 69 (13), 57 (100), 41 (14).

Diethyl 2-(1-phenoxypropan-2-yl)malonate (3ma, Scheme 3): Prepared according to *GPB*, after 85 h, but in this case, after 48 h, another portion of photocatalyst (5.2 mg, 2.5 mol %) and more of phenoxyacetic acid (230 mg, 1.5 mmol) were added. It was purified by FC (Hexane/EtOAc 97:3 to 90:10) and obtained as a colorless oil (96 mg, 0.325 mmol, 65%): TLC R_f 0.10 (Hexane/EtOAc 97:3); IR *v* 1741, 1369, 1234, 1035, 752 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.23 (m, 2H), 6.98 - 6.84 (m, 3H), 4.28 - 4.13 (m, 4H), 4.04 - 3.90 (m, 2H), 3.59 (d, *J* = 7.7 Hz, 1H), 2.85 - 2.69 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.8 (C), 168.7 (C), 158.9 (C), 129.5 (2 × CH), 120.9 (CH), 114.7 (2 × CH), 70.2 (CH_2), 61.5 (CH_2), 61.4 (CH_2), 54.2 (CH), 33.6 (CH), 15.0 (CH_3), 14.2 (CH_3), 14.1 (CH_3); GC R_T 17.778 min; LRMS (EI) *m/z* (%) = 249 (M^+ - C_2H_5O), 203 (38), 202 (11), 201 (100), 173 (50), 145 (51), 138 (22), 127 (89), 109 (11), 99 (10), 94 (30), 83 (38), 57 (32), 69 (11), 55 (22); HRMS (EI) *Calcd.* for $C_{16}H_{22}O_5$ 294.1467, found 294.1476.

Diethyl 2-(1-(*p*-tolyloxy)propan-2-yl)malonate (3na, Scheme 3): Prepared according to *GPB*, after 50 h. It was purified by FC (Hexane/EtOAc 97:3 to 90:10) and obtained as a colorless oil (142 mg, 0.46 mmol, 92%): TLC R_f 0.10 (Hexane/EtOAc 97:3), visualized by exposure to UV light; IR v 1738, 1507, 1236, 1174, 1034, 812 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.07 - 7.04 (m, 2H), 6.79 - 6.76 (m, 2H), 4.24 - 4.13 (m, 4H), 3.98 - 3.87 (m, 2H), 3.58 (d, *J* = 7.7 Hz, 1H), 2.81 - 2.66 (m, 1H), 2.27 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.14 (d,

J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ* 168.8 (C), 168.7 (C), 156.8 (C), 130.1 (C), 130.0 (2 × CH), 114.6 (2 × CH), 70.4 (CH_2), 61.5 (CH_2), 64.4 (CH_2), 54.2 (CH), 33.7 (CH), 20.6 (CH_3), 14.9 (CH_3), 14.2 (CH_3), 14.17 (CH_3); GC R_T 18.585 min; LRMS (EI) *m/z* (%) = 308 (M+, 4), 263 (10), 217 (28), 202 (11), 201 (100), 173 (56), 148 (11), 145 (51), 127 (82), 109 (11), 108 (35), 107 (18), 99 (11), 91 (18), 83 (30), 55 (14); HRMS (EI) *Calcd.* for $C_{17}H_{24}O_5$ 308.1624, found 308.1634.

Diethyl 2-(1-oxo-1-phenylpropan-2-yl)malonate (3oa, Scheme 3): Prepared according to *GPB*, after 38 h, but in this case 1 equiv. of ketoacid was added and after 8 h, another 1 equiv. was added. It was purified by FC (Hexane/EtOAc 95:5 to 90:10) and obtained as a pale yellow oil (98 mg, 0.335 mmol, 67%): TLC R_f 0.15 (Hexane/EtOAc 97:3); IR *v* 2977, 1744, 1727, 1681, 1457, 1288, 1179, 1024, 981, 714 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* 8.04 - 7.99 (m, 2H), 7.63 - 7.55 (m, 1H), 7.53 - 7.45 (m, 2H), 4.36 - 4.05 (m, 5H), 3.99 (d, *J* = 10.8 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 7.3 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H);^{13}C-NMR (75 MHz, $CDCl_3$) *δ* 201.7 (C), 168.9 (C), 168.5 (C), 135.7 (C), 133.4 (CH), 128.8 (2 x CH), 128.7 (2 x CH), 61.8 (2 ×CH_2), 56.4 (CH), 40.6 (CH), 16.0 (CH_3), 14.3 (CH_3), 14.0 (CH_3); GC R_T 17.797 min; LRMS (EI) *m/z* (%) = 247 (M^+ - C_2H_5O, 5), 201 (7), 106 (8), 105 (100), 77 (18).

Diethyl 2-(3-oxopentan-2-yl)malonate (3pa, Scheme 3): Prepared according to *GPB*, after 69 h, but in this case another portions of photocatalyst (1 mol %, 2.08 mg) and Na_2CO_3 (1 equiv., 0.5 mmol, 53 mg) were added after 48 h of reaction. Moreover, in this case 4 x 1 equiv. (207 mg, 2 mmol) of 2-ketobutyric acid were added every 12 h. It was purified by FC (Hexane/EtOAc 97:3 to 85:15) and obtained as a pale yellow oil (66 mg, 0.27 mmol, 54%): TLC R_f 0.10 (Hexane/EtOAc 97:3); IR *v* 1746, 1720, 1264, 1090, 1046, 916, 732 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* 4.27 - 4.08 (m, 4H), 3.77 (d, *J* = 10.6 Hz, 1H), 3.28 (dq, *J* = 10.6 Hz, 7.2 Hz, 1H), 2.63 (qd, *J* = 7.3, 3.2 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ* 212.3 (C), 168.8 (C), 168.7 (C), 61.8 (CH_2), 61.7 (CH_2), 54.7 (CH), 44.8 (CH), 34.8 (CH_2), 15.0 (CH_3), 14.3 (CH_3), 14.1 (CH_3), 7.8 (CH_3); GC R_T 13.745 min ; LRMS (EI) *m/z* (%) = 215 (M^+ - C_2H_5, 51), 200 (76), 189 (89), 188 (17), 187 (93), 171 (11), 169 (10), 159 (11), 154 (94), 143 (25), 142 (47), 122 (21), 115 (53), 114 (11), 113 (23), 99 (14), 87 (29), 86 (14), 68 (43), 57 (89); HRMS (EI) *Calcd.* for $C_{12}H_{20}O_5$ - C_2H_5 215.0919, found 215.0921.

Tandem decarboxylation-Giese reaction-lactonization (Scheme 5a).

Ethyl (3*S, 4*R**)-4, 5, 5-trimethyl-2-oxotetrahydro-2*H*-pyran-3-carboxylate ((±)-*trans*-3ra):** Prepared according to *GPB*, after 14 h. It was purified by FC (Hexane/EtOAc 95:5 to 80:20) and obtained as a pale yellow oil (86 mg, 0.40 mmol, 80%, >98:2 *dr* according ^{1}H and ^{13}C-NMR): TLC R_f 0.10 (Hexane/EtOAc 95:5); IR *v* 2977, 1724, 1481, 1379, 1249, 1174, 1154, 1090, 1046 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* 4.24 (q, *J* = 7.1 Hz, 2H), 4.09 (d, *J* = 11.1 Hz, 1H), 3.97 (d, *J* = 11.1 Hz, 1H), 3.18 (d, *J* = 11.4 Hz, 1H), 2.17 (dq, *J* = 11.4, 6.8 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.98 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.96 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) *δ* 169.5 (C), 167.3 (C), 79.8 (CH_2), 62.0 (CH_2), 53.8 (CH), 40.0 (CH), 32.5 (C), 23.5 (CH_3), 17.4 (CH_3), 14.2 (CH_3), 14.1 (CH_3); GC R_T 15.882 min; LRMS (EI) *m/z* (%) = 214 (M^+, 6), 199 (13), 169 (32), 159 (10), 155 (18), 142 (13), 141 (91), 127 (15), 125 (16), 123 (12), 115 (55), 113 (18), 109 (23), 97 (37), 96 (21), 95 (26), 87 (45), 83 (27), 82 (23), 81 (18), 70 (100), 69 (73), 67 (16), 56 (30), 55 (69); HRMS (DIP) *Calcd.* for $C_{11}H_{18}O_4$ – CH_3 199.0970, found 199.0977.

***β*-Fragmentation after addition of 1q to 2a (Scheme 5b).**

Diethyl 2-(1-((3,4-dichlorophenyl)thio)ethyl)malonate (5): Prepared according the *GPB*, after 24 h. It was purified by FC (Hexane/EtOAc 95:5 to 90:10) and obtained as a colorless oil (135 mg, 0.37 mmol, 74%): TLC R_f 0.28 (95:5 Hexane/EtOAc); IR *v* 2989, 1730, 1456, 1258, 1219, 1133, 1050, 1025, 809 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* 7.58 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.32 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.75 (dq, *J* = 8.6, 6.9 Hz, 1H), 3.48 (d, *J* = 8.6 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ* 167.5 (C), 167.2 (C), 134.9 (CH), 133.7 (C), 133.0 (C), 132.7 (CH), 132.5 (C), 130.8 (CH), 62.0 (CH_2), 61.9 (CH_2), 57.7 (CH), 43.5 (CH), 19.5 (CH_3), 14.2 (2 x CH_3); LRMS (DIP) *m/z* (%) = 368 (M^{+37}Cl, 12), 367 (10), 366 (63), 365 (16), 364 (M^{+} $^{+35}$Cl, 87), 247 (32), 245 (42), 217 (31), 207 (49), 205 (68), 179 (48), 178 (39), 177 (64), 142 (77), 141 (100), 135 (39), 113 (46), 97 (31), 95 (32), 87 (51), 85 (67), 73 (58), 69 (97), 57 (40), 55 (38), 43 (34), 41 (46); HRMS (DIP) *Calcd.* for $C_{15}H_{18}Cl_2O_4S$ 364.0303, found 364.0301.

1, 2-bis(3,4-dichlorophenyl)disulfane (6, Scheme 5b):[30] Compound **6** was obtained as side-product of **5**, following the procedure described above. It was purified by FC (Hexane/EtOAc 97:3) and obtained as a white solid (45 mg, 0.13 mmol, 17%): TLC R_f 0.65 (Hexane/EtOAc 97:3); IR *v* 2913, 1563, 1454, 1362, 1143, 1117, 1084, 1030, 858, 799, 675 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* 7.56 (d, *J* = 2.1 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.29 (dd, *J* = 8.4, 2.2 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ* 136.3 (2 x C), 133.6 (2 x C), 132.1 (2 x C), 131.1 (2 x CH), 129.3 (2 x CH), 127.0 (2 x CH); GC R_T 25.335 min; LRMS (EI) *m/z* (%) = 360 (M^{+37}Cl, 11), 358 (40), 357 (11), 356 (M^{+35}Cl, 72), 354 (54), 179 (69), 177 (100), 144 (30), 142 (76).

Radical Cascade of Homoallylic Acid 1s with 2a (Scheme 5c)

Diethyl (2*S*,5*R*)-5-(4-ethoxy-3-(ethoxycarbonyl)-2-methyl-4-oxobutyl)-2,3,3- trimethylcyclopentane- 1, 1- dicarboxylate (7): Prepared according to *GPB*, after 24 h, but in this case the reaction was performed employing 1 equiv. of homoallylic acid **1s** (65 mg, 0.5 mmol) and 2.5 equiv. of **2a** (235 mg, 1.25 mmol). It was purified by FC (97:3 to 90:10 Hexane/EtOAc) and obtained as a colorless oil (148 mg, 0.33mmol, 65%, 1:1 *dr* according NMR and GC experiments): TLC R_f 0.2 (Hexane/EtOAc 95:5); IR *v* 2978, 1727, 1366, 1243, 1179, 1036, 856 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *mixture of diastereoisomers δ* 4.30 - 4.07 (m, 8H), 3.34 (d, *J* = 5.9 Hz, 0.40H), 3.16 (d, *J* = 8.4 Hz, 0.40H), 3.09 - 2.94 (m, 1H), 2.66 (q, *J* = 7.4 Hz, 1H), 2.36 - 2.12 (m, 1H), 1.78 (p, *J* = 6.2 Hz, 1H), 1.71 - 1.53 (m, 1H), 1.30 - 1.21 (m, 13H), 1.07 - 0.99 m, 7H), 0.88 (d, *J* = 3.2 Hz, 1.50H), 0.86 (d, *J* = 3.2 Hz, 1.50H), 0.98 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *mixture of diastereoisomers δ* 172.0 (C), 171.8 (2 × C), 171.7 (C), 169.3 (C), 168.8 (C), 168.7 (C), 168.6 (C), 67.7 (C), 67.6 (C), 61.32 (CH_2), 61.27 (2 × CH_2), 61.13 (CH_2), 61.07 (CH_2), 61.0 (CH_2), 60.94 (CH_2), 60.87 (CH_2), 58.8 (CH), 56.1 (CH), 49.5 (CH), 49.2 (CH), 47.2 (CH_2), 45.7 (CH_2), 41.3 (CH), 40.6 (CH), 40.2 (C), 40.1 (C), 37.2 (CH), 36.5 (CH), 32.3 (CH_3), 31.8 (CH_3), 29.21 (CH_3), 29.17 (CH_3), 22.8 (CH_3), 22.6 (CH_3), 18.1 (CH_3), 16.4 (CH_3), 14.21 (5 × CH_3), 14.15 (CH_3), 11.62 (CH_3), 11, 57 (CH_3); GC R_T 22.008 min and 22.224 min (*two diastereoisomers)*; LRMS (EI) *m/z (diastereoisomer A)* (%) = 411 (M+ - C_2H_5, 9), 337 (25), 297 (43), 222 (19), 196 (21), 187 (100), 149 (44), 141 (50), 107 (19), 69 (19); *m/z (diastereoisomer B)* (%) = 411 (M^+ - C_2H_5O, 15), 337 (38), 336 (20), 297 (45), 205 (24), 196 (19), 187 (100), 149 (45), 141 (50), 107 (19), 69 (19); HRMS (EI) *Calcd.* for $C_{24}H_{40}O_8$ - C_2H_5O 411.2383 found 411.2392.

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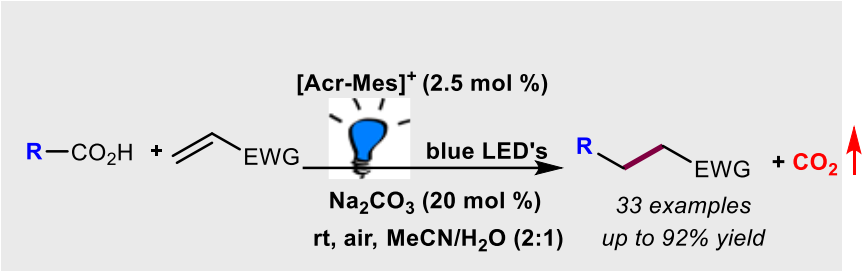

Synthetic Methods

*Nieves P. Ramirez, Jose C. Gonzalez-Gomez**

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Decarboxylative Giese-type reaction of carboxylic acids promoted by visible-light: a sustainable and photoredox neutral protocol.

The decarboxylative alkylation of carboxylic acids can be efficiently conducted under air atmosphere, at room temperature, using [Acr-Mes]$^+$ as photocatalyst and promoted by visible-light. A range of readily available starting materials has been well tolerated with this transition-metal-free protocol.