1,7-Octadiene-Assisted Tandem Multicomponent Cross-Enyne Metathesis (CEYM)-Diels-Alder Reactions: A Useful Alternative to Mori's Conditions

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Abstract: The use of 1,7-octadiene as an in situ source of ethylene led us to develop a novel multicomponent tandem cross-enyne metathesis (CEYM)-Diels–Alder reaction. The process can be considered a relay metathesis, in which the ethylene liberated in the ring-closing metathesis (RCM) of 1,7-octadiene initiates the tandem sequence. Aliphatic, aromatic, and fluorinated alkynes and several dienophiles are compatible with the process, which is particularly efficient with aromatic alkynes. This methodology constitutes a useful variant of Mori's conditions in CEYM-related reactions.

Keywords: cross metathesis • Diels–Alder reactions • multicomponent reactions • octadienes • tandem reactions

Introduction

Metathesis has become one of the most powerful tools for the creation of carbon–carbon bonds.^[1] With the advent of stable ruthenium catalysts, metathesis processes have become the transformation of choice for the creation of a wide variety of carbo- and heterocycles.^[2] Among them, enyne metathesis (EYM) is a singular process as a new functionality in the product that is different from that of the starting materials is generated.^[3] This reorganization of an alkene and alkyne to produce a 1,3-diene was first reported in 1985.^[4] However, its development has lagged behind its diene counterpart, probably due to the less predictable nature of its regio- and stereoselectivity.^[5]

EYM has been used in both intra- (ring-closing enyne metathesis, RCEYM) and intermolecular (cross-enyne metathesis, CEYM) applications. Whereas examples of RCEYM are well-documented in the literature,^[6] the intermolecular CEYM has seen fewer applications because of its greater difficulty (the first example of CEYM was reported in early 1997).^[7] The discovery of the beneficial effect of ethylene by Mori et al. has changed this tendency, allowing for the preparation of 1,3-dienes^[8] suitable for either interor intramolecular Diels–Alder reactions in a sequential or tandem manner.^[9] This metathesis cascade chemistry is a powerful tool for the synthesis of skeletally diverse small molecules, converting the diene created through enyne metathesis into other useful functionalities and increasing

[a] Prof. Dr. S. Fustero, P. Bello, J. Miró, Prof. Dr. A. Simón, Prof. Dr. C. del Pozo Departamento de Química Orgánica Universidad de Valencia 46100-Burjassot, Valencia (Spain) Fax: (+34)963-544-939 E-mail: santos.fustero@uv.es carlos.pozo@uv.es the molecular complexity with minimal added cost or waste. $\ensuremath{^{[10]}}$

In this context, during the course of an on-going project in our laboratory aimed at the development of a new CEYM-Diels–Alder protocol, we discovered that the ethylene generated in the RCM of 1,7-octadiene can serve as an in situ source of ethylene and initiates the aforementioned sequence. This serendipitous finding led us to develop a multicomponent cascade reaction that allows for the synthesis of new carbo- and heterocyclic derivatives in a tandem protocol. This methodology was further extended to fluorinated alkynes (Scheme 1).



Scheme 1. 1,7-Octadiene promoted tandem multicomponent CEYM-Diels-Alder reaction.

Results and Discussion

Our initial idea was the development of a new triple tandem protocol: a combination of a CEYM/CM/Diels–Alder reaction.^[11] Thus, CEYM of an alkyne and an 1,n-diene would render a new 1,3-diene functionality bearing an additional double bond suitable for a subsequent CM reaction that would convert this olefin into a good dienophile for an intramolecular Diels–Alder reaction (Scheme 2, pathway A). To this end, phenyl acetylene **1a** was chosen as a model substrate and was subjected to the tandem protocol by treatment with ruthenium catalyst **I** (5 mol%) in the presence of

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CEYM = Cross enyne metathesis **IMDAR** = Intramolecular Diels-Alder reaction **CM** = Cross metathesis

Scheme 2. Reaction of **1a** with 1,7-cyclooctadiene and ethyl acrylate in the presence of ruthenium catalyst **Ru-I**.

1,7-octadiene and ethyl acrylate. However, when this mixture was heated in toluene at 90°C for 6 h, instead of the expected bicyclic derivative (Scheme 2, pathway A) a regioisomeric mixture of compounds 3a and 3a' was isolated in an excellent yield (90%) in a 82:18 ratio (Scheme 2, pathway B). This result indicates that the ring-closing metathesis reaction of 1,7-octadiene is more favorable than the crossmetathesis protocol. Therefore, after the RCM of 1,7-octadiene, cyclohexadiene and ethylene are liberated and the ruthenium carbene as the catalytic species is released. This carbene reacts with the triple bond in a cross-metathesis

Abstract in Spanish: El empleo de 1,7-octadieno como una fuente in situ de etileno nos ha permitido desarrollar un nuevo proceso tándem multicomponente metátesis cruzada de enino-reacción de Diels–Alder. El proceso puede considerarse como una metátesis por relevos, donde el etileno liberado en la metátesis con cierre de anillo del 1,7-octadieno inicia la secuencia tándem. Alquinos alifáticos, aromáticos y fluorados y varios dienófilos son compatibles con el proceso, que es particularmente eficiente con alquinos aromáticos. Esta metodología constituye una variante útil de las condiciones desarrolladas por Mori en reacciones de metátesis cruzada de eninos. ChemPubSoc

fashion, generating a new carbene that in turn would react with the previously formed ethylene to afford intermediate diene **2a**. Under the reaction conditions, in the presence of ethyl acrylate, diene **2a** would be trapped in a Diels–Alder fashion to afford regioisomers **3a** and **3a'**. This would be similar to a relay metathesis process,^[12] in which the remote initiating site is used to release both the ruthenium carbene as the active catalyst and the ethylene for the subsequent CEYM by extruding cyclohexene. The overall process constitutes a novel tandem multicomponent CEYM-Diels– Alder reaction and, therefore, we decided to evaluate this protocol in more detail.

In the first step of our study we evaluated the formation of 1,3-diene **2a** in the presence of 1,7-octadiene. Thus, when phenylacetylene **1a** was heated with 1,7-octadiene as the internal source of ethylene in the presence of ruthenium catalyst **I** in toluene at 90 °C, complete formation of the diene was observed after two hours (determined by TLC analysis). Under these conditions, diene **2a** was isolated in 98% yield after flash chromatography (Scheme 3).

With these data in hand we decided to identify suitable conditions for the tandem multicomponent CEYM-Diels-



Scheme 3. Formation of diene 2a.



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Alder reaction by trapping the dienic intermediate with a variety of dienophiles present in the reaction vessel. The reaction described in Scheme 2 with ethyl acrylate as a dienophile was employed as the starting point. When this reaction mixture was heated in toluene at 90 °C and allowed to react for 20 h, a mixture of the regioisomers **3a/3a'** was obtained in quantitative yield (Table 1, entry 1). Therefore, these conditions were further extended to different starting alkynes **1** and dienophiles. The results are summarized in Table 1.

Several dienophiles were tested in the tandem protocol; besides ethyl acrylate, ethyl fumarate and 1,4-benzoquinone gave the desired products **3b** and **3e**, respectively, also in quantitative yield (Table 1, entries 2 and 5). Diethyl acetylendicarboxylate (DEADC) gave rise to the final product **3c** in 70% yield and no aromatization was observed during the purification process (entry 3). *N*-Phenyl maleimide was also a good partner for the tandem process, affording cycloadduct **3d** in 62% yield (entry 4). With aromatic alkynes the tandem protocol proceeded with excellent efficiency, afford-

Table 1. Preparation of cycloadducts **3** by tandem multicomponent CEYM-Diels-Alder reactions of substrates **1** and 1,7-octadiene.



Entry	Substrate	R	Dienophile	<i>t</i> [h]	Product	Yield [%] ^[a]					
1	1a	Ph	CO ₂ Et	20	3a+3a'	99 ^[b]					
2	1a	Ph	EtO ₂ C CO ₂ Et	20	3 b	98					
3	1a	Ph	$EtO_2C - CO_2Et$	20	3 c	70					
4	1a	Ph	N - Ph	20	3 d	62					
5	1a	Ph		20	3e	99					
6	1b	4-MeO-C ₆ H ₄	EtO ₂ C CO ₂ Et	20	3 f	99					
7	1c	2-MeO-C ₆ H ₄	EtO ₂ C CO ₂ Et	20	3 g	99					
8	1d	4-F-C ₆ H ₄	EtO ₂ C CO ₂ Et	20	3h	99					
9	1e	2,4-F ₂ -C ₆ H ₃	EtO ₂ C CO ₂ Et	20	3i	86					
10	1f	3,4-F ₂ -C ₆ H ₃	EtO ₂ C CO ₂ Et	20	3j	99					
11	1g	$4-CF_3-C_6H_4$	EtO ₂ C CO ₂ Et	20	3k	99					
12	1 h	3,5-(CF ₃) ₂ -C ₆ H ₃	EtO ₂ C CO ₂ Et	30	31	95					
13	1i	3-pyridyl	EtO ₂ C CO ₂ Et	22	3 m	50					
14	1j	CH ₂ OAc	EtO ₂ C CO ₂ Et	28	3 n	42					
15	1 k	MeO ₂ C	EtO ₂ C CO ₂ Et	20	30	46 ^[c]					
16	11	TIPS	EtO ₂ C CO ₂ Et	72	3 p	31					

[a] The yields shown in the table were obtained with 4 equivalents of 1,7-octadiene. [b] Compounds 3a/3a' were obtained as a 82:18 mixture of regiosiomers, as determined by GC-MS. [c] When methyl propiolate was used as the starting alkyne compound 4 (see Scheme 4) was isolated in 30% yield together with the desired product. TIPS = triisopropylsilyl.

ing the final adducts in excellent yields; either phenyl acetylene (entry 2) or aromatic alkynes with electron-donating (entries 6 and 7) or -withdrawing substituents (entries 8–12) reacted with ethyl fumarate in almost quantitative yields in most cases. However, with heteroaromatic alkynes (entry 13), aliphatic alkynes (entry 14), or electronically deficient alkynes (entry 15) the overall process was less effective affording the final products in moderate yields. It is worth mentioning that the reaction also took place with the very sterically demanding triisopropylsilyl acetylene, albeit the desired adduct was isolated in a modest 31 % yield after 72 h (entry 16).

When methyl propiolate was used as the starting alkyne in the tandem protocol, together with the desired product 3o (46%), compound 4 was isolated in 30% yield (Scheme 4). This product arises from the highly regioselec-



Scheme 4. Multicomponent reaction with methyl propiolate 1k.

tive Diels-Alder reaction of two molecules of the dienic intermediate, initially formed by CEYM reaction of methyl propiolate with the ethylene generated in situ, one of them acting as the diene counterpart and the other one as a dienophile for the most electronically deficient olefin (Scheme 4). In the presence of ethyl fumarate, this process competes with the Diels-Alder reaction of this diene intermediate with ethyl fumarate, which generates adduct 30. With this data in hand, we decided to perform the process in the absence of ethyl fumarate. Thus, after 22 h under the optimized conditions, compound 4 was isolated in 70% yield in a regioselective fashion (Scheme 4).^[13] This unexpected reaction extends the utility of this tandem protocol.

The results summarized in Table 1 showed that this multicomponent tandem protocol is a useful alternative to Mori's conditions in CEYM-type processes.^[8] The use of 1,7-octadiene as an in situ source of ethylene gas represents a logistical improvement. Following our ongoing interest in the use of fluorinated building blocks,^[14] we decided to extend the scope of this transformation to fluorinated deriva-

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tives **5**.^[15] In this context, several fluorinated terminal alkynes were subjected to the optimized reaction conditions. The results obtained in this study are depicted in Table 2.

Difluoropropargyl amide $5a^{[16]}$ reacted with ethyl fumarate to give adduct 6a in 70% yield (Table 2, entry 1). DEADC afforded diene 6b in its reaction with 5a in moderate yield, and no aromatization was observed during the purification process (entry 2). *N*-Phenyl maleimide and *p*-ben-

Table 2. Preparation of difluorinated cycloadducts **6** by tandem multicomponent CEYM-Diels-Alder reactions of substrates **5** and 1,7-octadiene.



Entry	Substrate	R	Dienophile	<i>t</i> [h]	Product	Yield [%] ^[a]
1	5a	PhCH ₂ NH	EtO ₂ C CO ₂ Et	20	6a	70
2	5a	PhCH ₂ NH	EtO ₂ C	6	6b	55
3	5a	PhCH ₂ NH	O N - Ph O	24	6c	63
4	5a	PhCH ₂ NH		24	6 d	50
5	5b	(R)-Ph(Me)CHNH	EtO ₂ C CO ₂ Et	24	6e+6e'	73 ^[b]
6	5b	(R)-Ph(Me)CHNH	N-Ph	10	6f+6f	70 ^[b]
7	5b	(R)-Ph(Me)CHNH	EtO ₂ C	24	6g	60
8	5c	Ph	EtO ₂ C — CO ₂ Et	15	6 h	55
9	5c	Ph	EtO ₂ C CO ₂ Et	17	6i	70

[a] The yields shown in the table were obtained with 4 equiv of 1,7-octadiene. [b] In these cases, adducts were obtained as an inseparable 1:1 mixture of diastereoisomers.



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zoquinone were also good partners for the tandem process, affording the cycloadducts **6c** and **6d** in 62 and 50% yields, respectively (entries 3 and 4). With chiral starting material **5b**, an 1:1 inseparable mixture of diastereoisomers was achieved in all cases, which indicates that the chiral information is too far away from the reacting center (entries 5–7). Finally, fluorinated ketones were also adequate substrates for the sequential process (entries 8 and 9) and again the reaction

with DEADC afforded product **6h** without aromatization. Therefore, by following this methodology, a new family of fluorinated carbo- and heterocycles can be created in a simple manner.^[17]

Conclusion

A novel multicomponent tandem enyne cross-metathesis-Diels-Alder reaction of terminal alkynes with a variety of nucleophiles was developed. The process relies on the use of 1,7-octadiene as an in situ source of ethylene by RCM, allowing the initial formation of the 1,3-diene by its reaction with the starting alkyne and initiating the tandem sequence. The developed methodology was particularly efficient with aromatic alkynes. This protocol constitutes an alternative to the Mori's conditions avoiding the use of ethylene gas. Further applications of this tandem protocol are currently underway.

Experimental Section

General methods: Reactions were carried out under an argon atmosphere unless otherwise indicated. The solvents were purified prior to use: THF, diethyl ether, and toluene were distilled from sodium/benzophenone; dichloromethane was distilled from calcium hydride. The reactions were monitored with the aid of TLC on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicat-

ed solvents on silica gel 60 (particle size: 0.040–0.063 mm). Melting points were measured on a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1020 polarimeter. ¹H, ¹⁹F, and ¹³C NMR spectra were recorded on a 300 or 400 MHz spectrometer. Chemical shifts are given in ppm (δ), with reference to the residual proton resonances of the solvents. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br indicate that the signal is broad.

General procedure for the multicomponent tandem protocol: A solution of catalyst I (5 mol%), 1,7-octadiene (4 equiv), alkyne 1 (0.5 mmol), or 5 (0.12 mmol) and the corresponding dienophile (3 equiv) in dry toluene (0.05 M) was heated at 90 °C in a sealed tube. The reaction mixture was stirred at this temperature until TLC analysis showed total consumption of the starting material (times are shown in Tables 1 and 2). The solvents were then removed under reduced pressure and the crude mixture was purified by flash chromatography in hexanes/ethyl acetate.

2-Phenyl-1,3-butadiene (2a): By following the general procedure described above and before adding the dienophile, the crude mixture was subjected to flash chromatography affording $2a^{[18]}$ (65 mg, 98% yield) as a colorless oil by starting from 51 mg of phenyl acetylene 1a.

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Ethyl 3-phenyl-3-cyclohexene carboxylate and ethyl 4-phenyl-3-cyclohexene carboxylate (3a/3a'): By following the general procedure described above, an inseparable mixture of regioisomers 3a/3a' ^[19] (115 mg, 82:18, 99% yield) were obtained as a yellowish oil by starting from 51 mg of 1a.

(*trans*)-Diethyl 4-phenyl-4-cyclohexene-1,2-dicarboxylate (3b): By following the general procedure described above, $3b^{[19]}$ (148 mg, 98% yield) was obtained as a yellowish oil by starting from 51 mg of 1a.

Diethyl 4-phenyl-1,4-cyclohexadiene dicarboxylate (3c): By following the general procedure described above, **3c** (105 mg, 70% yield) was obtained as a yellowish oil by starting from 51 mg of **1a**. ¹H NMR (CDCl₃, 300 MHz): δ =1.24 (t, *J*=6 Hz, 3H), 1.25 (t, *J*=6 Hz, 3H), 3.11–3.19 (m, 2H), 3.29–3.35 (m, 2H), 4.19 (q, *J*=6 Hz, 2H), 4.20 (q, *J*=6 Hz, 2H), 6.00–6.03 (m, 1H), 7.16–7.34 ppm (m, 5H); ¹³C NMR (CDCl₃, 300 MHz): δ =14.0 (s, 2CH₃), 29.1 (s, CH₂), 29.7 (s, CH₂), 61.1 (s, CH₂), 61.2 (s, CH₂), 119.2 (s, CH), 125.0 (s, 2CH), 127.5 (s, CH), 128.4 (s, 2CH), 131.8 (s, C), 132.5 (s, C), 132.6 (s, C), 139.9 (s, C), 167.8 (s, C), 167.9 ppm (s, C); HRMS: *m/z*: calcd for C₁₈H₁₉O₄: 209.1278 [*M*–2]⁺; found: 209.1287.

2,5-Diphenyl-3a,4,7,7 a-tetrahydro-1*H***-isoindole-1,3-2***H***-dione** (3d): By following the general procedure described above, 3d (94 mg,¹¹⁹) 62 % yield) was obtained as a yellowish oil by starting from 51 mg of 1a.

2-Phenyl-1,4,4,a,9 a-tetrahydroanthracene-9,10-dione (3e): By following the general procedure described above, **3e** (143 mg, 99% yield) was obtained as a yellowish oil by starting from 51 mg of **1a**. ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.36$ (d, J = 18 Hz, 1H), 2.53 (d, J = 17 Hz, 1H), 2.64 (d, J = 18 Hz, 1H), 2.85 (d, J = 17 Hz, 1H), 3.35 (dd, $J_1 = 11$ Hz; $J_2 = 6$ Hz, 1H), 3.46 (dd, $J_1 = 11$; $J_2 = 6$ Hz, 1H), 5.98 (s, 1H), 7.11–7.28 (m, 5H), 7.65 (dd, $J_1 = 5$; $J_2 = 3$ Hz, 2H), 7.96 ppm (d, J = 3 Hz, 2H); ¹³C NMR (CDCl₃, 300 MHz): $\delta = 25.3$ (s, CH₂), 26.7 (s, CH₂), 46.1 (s, CH), 47.0 (s, CH), 121.5 (s, CH), 125.2 (s, 2CH), 126.8 (s, CH), 126.9 (s, CH), 127.1 (s, CI), 128.2 (s, 2CH), 133.9 (s, C), 134.3 (s, 2CH), 134.7 (s, C), 141.0 (s, C), 197.7 (s, C), 198.0 ppm (s, C); HRMS: m/z: calcd for C₂₀H₁₇O₂: 289.1223 [M+1]⁺; found: 289.1232.

(*trans*)-Diethyl **4-(4-methoxyphenyl)-4-cyclohexene-1,2-dicarboxylate** (**3 f**): By following the general procedure described above, **3 f** (164 mg, 99% yield) was obtained as a yellowish oil by starting from 66 mg of **1 b**. ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.26$ (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.29–2.41 (m, 1H), 2.47–2.66 (m, 2H), 2.76–2.84 (m, 1H), 2.85–3.04 (m, 2H), 3.79 (s, 3H), 4.16 (q, J = 7.1 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 5.97 (t, J = 2.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 7.29 ppm (d, J = 8.7 Hz, 2H); ¹³C NMR (CDCl₃, 300 MHz): $\delta = 14.1$, 1 (s, 2CH₃), 28.6 (s, CH₂), 30.2 (s, CH₂), 41.1 (s, CH), 42.0 (s, CH), 55.2 (s, CH₃), 60.6 (s, CH₂), 60.6 (s, C), 174.7 (s, C), 174.6 (s, C), 174.7 ppm (s; C); HRMS: m/z: calcd for C₁₉H₂₅O₅: 333.1697 [M+1]⁺; found: 333.1700.

(*trans*)-Diethyl **4-(2-methoxyphenyl)-4-cyclohexene-1,2-dicarboxylate** (**3g**): By following the general procedure described above, **3g** (165 mg, 99% yield) was obtained as a yellowish oil by starting from 66 mg of **1c**. ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.24$ (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 2.29–2.39 (m, 1H), 2.53–2.75 (m, 3H), 2.90–3.03 (m, 2H), 3.78 (s, 3H), 4.09–4.21 (m, 4H), 5.72–5.74 (m, 1H), 6.83–6.91 (m, 2H), 7.09 (dd, $J_1=7.4$, $J_2=1.9$ Hz, 1H), 7.19–7.25 ppm (m, 1H); ¹³C NMR (CDCl₃, 300 MHz): $\delta = 14.0$, (s, 2CH₃), 28.5 (s, CH₂), 31.4 (s, CH₂), 41.0 (s, CH), 41.9 (s, CH), 55.2 (s, CH₃), 60.3 (s, CH₂), 60.4 (s, CH₂), 110.5 (s, CH), 120.4 (s, CH), 123.4 (s, CH), 128.3 (s, CH), 129.4 (s, CH), 131.6 (s, C), 135.7 (s, C), 156.5 (s, C), 174.7 (s, C), 174.8 ppm (s, C); HRMS: m/z: calcd for C₁₉H₂₅O₅: 333.1697 [M+1]⁺; found: 333.1703.

(*trans*)-Diethyl 4-(4-fluorophenyl)-4-cyclohexene-1,2-dicarboxylate (3h): By following the general procedure described above, 3h (159 mg, 99% yield) was obtained as a yellowish oil by starting from 60 mg of 1d. ¹H NMR (CDCl₃, 300 MHz): δ =1.27 (t, *J*=7.1 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H), 2.32–2.42 (m, 1H), 2.49–2.67 (m, 2H), 2.73–2.81 (m, 1H), 2.86–3.05 (m, 2H), 4.17 (q, *J*=7.1 Hz, 2H), 4.18 (q, *J*=7.1 Hz, 2H), 6.00 (t, *J*=2.4 Hz, 1H), 6.99 (dd, *J*₁=*J*₂=8.7 Hz, 2H), 7.31 ppm (dd, *J*₁=8.7, *J*₂=5.4 Hz, 2H); ¹³C NMR (CDCl₃, 300 MHz): δ =14.0, (s, 2CH₃), 28.4 (s, CH₂), 30.1 (s, CH₂), 40.9 (s, CH), 41.8 (s, CH), 60.8 (s, CH₂), 60.6 (s, CH₂), 115.0 (d, ²*J*(C,F)=21.3 Hz, 2CH), 121.8 (s, CH), 126.6 (d, ³*J*(C,F)=7.9 Hz, 2CH), 134.1 (s, C), 136.8 (s, C), 162.0 (d, ¹*J*(C,F)=246.3 Hz, CF), 174.3 (s, C), 174.4 ppm (s, C); ¹⁹F NMR (CDCl₃, 282 MHz): $\delta = -115.9$ ppm (s, 1F); HRMS: m/z: calcd for C₁₈H₂₂FO₄: 321.1497 [*M*+1]⁺; found: 321.1491.

(*trans*)-Diethyl 4-(2,4-difluorophenyl)-4-cyclohexene-1,2-dicarboxylate (3i): By following the general procedure described above, 3i (145 mg, 86% yield) was obtained as a yellowish oil by starting from 69 mg of 1e. ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.23$ (t, J = 7.0 Hz, 3H), 1.24 (m, J =7.2 Hz, 3H), 2.29-2.40 (m, 1H), 2.49-2.70 (m, 3H), 2.87-3.02 (m, 2H), 4.10-4.19 (m, 4H), 5.84-5.85 (m, 1H), 6.71-6.82 (m, 2H), 7.11-7.19 ppm (m, 1 H); ${}^{13}C$ NMR (CDCl₃, 300 MHz): $\delta = 14.1$, (s, 2 CH₃), 28.3 (s, CH₂), 31.0 (d, ${}^{5}J(C,F) = 3.0$ Hz, CH₂), 40.7 (s, CH), 41.65 (s, CH), 60.6 (s, CH₂), 60.7 (s, CH₂), 104.0 (t, ${}^{2}J(C,F) = 27.2$ Hz, CH), 111.0 (dd, ${}^{2}J_{CF} = 21.1$, ${}^{4}J_{CF} = 3.8$ Hz, CH), 125.6 (d, ${}^{4}J_{CF} = 2.3$ Hz, CH), 125.9 (d, ${}^{2}J_{CF} = 3.8$ Hz, C), 129.9 (dd, ${}^{3}J(C,F) = 9.1$, ${}^{3}J(C,F) = 6.0$ Hz, CH), 131.0 (d, ${}^{3}J(C,F) = 1.5$ Hz, C), 159.2 (dd, ${}^{1}J(C,F) = 160.1$, ${}^{3}J(C,F) = 12.1$ Hz, CF), 162.5 (dd, ${}^{1}J(C,F) =$ 158.5, ${}^{3}J$ (C,F)=12.1 Hz, CF), 174.3 (s, C), 174.5 ppm (s, C); ${}^{19}F$ NMR (CDCl₃, 282 MHz): $\delta = -111.5$ (d, ${}^{4}J(F,F) = 7.3$ Hz, 1F), -112.4 ppm (d, ${}^{4}J(F,F) = 7.3 \text{ Hz}, 1F$; HRMS: m/z: calcd for $C_{18}H_{21}F_{2}O_{4}$: 339.1402 [M+1]+; found: 339.1410.

(*trans*)-Diethyl **4-(3,4-difluorophenyl)-4-cyclohexene-1,2-dicarboxylate** (**3**): By following the general procedure described above, **3**j (167 mg, 99% yield) was obtained as a yellowish oil by starting from 69 mg of **1 f**. ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.23$ (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 2.28–2.74 (m, 3H), 2.82–3.01 (m, 2H), 4.10–4.18 (m, 4H), 5.99–6.00 (m, 1H), 7.01–7.14 ppm (m, 3H); ¹³C NMR (CDCl₃, 300 MHz): $\delta = 14.0$, (s, 2 CH₃), 28.3 (s, CH₂), 29.7 (s, CH₂), 40.7 (s, CH), 41.6 (s, CH), 60.6 (s, CH₂), 60.7 (s, CH₂), 113.9 (d, ²*J*(C,F)=17.4 Hz, CH), 116.8 (d, ²*J*-(C,F)=17.4 Hz, CH), 120.9 (dd, ³*J*(C,F)=6.0, ⁴*J*(C,F)=3.5 Hz, CH), 122.94 (d, ⁵*J*(C,F)=1.3 Hz, CH), 133.2 (s, C), 137.8 (dd, ³*J*(C,F)=5.6, ⁴*J*-(C,F)=3.9 Hz, C), 148.1 (dd, ¹*J*(C,F)=49.0, ²*J*(C,F)=13.3 Hz, CF), 151.3 (¹*J*(C,F)=49.0, ²*J*(C,F)=13.5 Hz, 1F), -140.4 ppm (d, ³*J*(F,F)=21.5 Hz, 1F); HRMS: *m/z*: calcd for C₁₈H₂₁F₂O₄: 339.1402 [*M*+1]⁺; found: 339.1400.

(*trans*)-Diethyl 4-(4-trifluoromethylphenyl)-4-cyclohexene-1,2-dicarboxylate (3k): By following the general procedure described above, 3k (183 mg, 99% yield) was obtained as a yellowish oil by starting from 85 mg of 1g. ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.24$ (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.32–2.44 (m, 1H), 2.51–2.69 (m, 2H), 2.73–2.81 (m, 1H), 2.86–3.04 (m, 2H), 4.11–4.20 (m, 4H), 6.12–6.13 (m, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.53 ppm (d, J = 8.2 Hz, 2H); ¹³C NMR (CDCl₃, 300 MHz): $\delta = 14.0$, (s, 2CH₃), 28.4 (s, CH₂), 29.7 (s, CH₂), 40.7 (s, CH), 41.6 (s, CH), 60.6 (s, CH₂), 60.7 (s, CH₂), 124.1(q, ¹J(C,F)=271.5 Hz, CF₃), 124.1 (s, CH), 125.1 (q, ³J(C,F)=3.7 Hz, 2CH), 125.2 (s, 2CH), 128.9 (q, ²J(C,F)=32.6 Hz, C), 134.0 (s, C), 144.1 (s, C), 174.2 (s, C), 174.3 ppm (s, C); ¹⁹F NMR (CDCl₃, 282 MHz): $\delta = -62.9$ ppm (s, 3F); HRMS: m/z: calcd for C₁₉H₂₂F₃O₄: 371.1465 [M+1]⁺; found: 371.1462.

(*trans*)-Diethyl **4-[3,5-bis(trifluoromethyl)phenyl]-4-cyclohexene-1,2-dicarboxylate (31):** By following the general procedure described above, **31** (207 mg, 95% yield) was obtained as a yellowish oil by starting from 119 mg of **1h**. ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.27$ (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 2.39–2.51 (m, 1H), 2.58–2.83 (m, 3H), 2.92–3.10 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 6.21–6.23 (m, 1H), 7.74 (s, 1H), 7.76 ppm (s, 2H); ¹³C NMR (CDCl₃, 300 MHz): $\delta = 14.1$, (s, 2CH₃), 28.2 (s, CH₂), 29.5 (s, CH₂), 40.6 (s, CH), 41.5 (s, CH), 60.9 (s, CH₂), 61.0 (s, CH₂), 120.7 (sept, ³*J*(C,F)=3.8 Hz, CH), 123.3 (q, ¹*J*(C,F)=272.5 Hz, 2CF₃), 125.2 (s, CH), 125.8 (s, 2CH), 131.7 (q, ²*J*-(C,F)=33.2 Hz, 2C), 133.1 (s, C), 142.9 (s, C), 174.0 (s, C), 174.1 ppm (s, C), (79 FNMR (CDCl₃, 282 MHz): $\delta = -63.4$ ppm (s, 6F); HRMS: *m/z*: calcd for C₂₀H₂₁F₆O₄: 439.1339 [*M*+1]⁺; found: 439.1341.

(*trans*)-Diethyl **4-(3-pyridy**)-**4-cyclohexene-1,2-dicarboxylate** (**3m**): By following the general procedure described above, **3m** (76 mg, 50% yield) was obtained as a yellowish oil by starting from 52 mg of **1i**. ¹H NMR (CDCl₃, 300 MHz): δ =1.26 (t, *J*=7.1 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H), 2.35–2.46 (m, 1H), 2.52–2.71 (m, 2H), 2.75–2.83 (m, 1H), 2.89–3.07 (m, 2H), 4.16 (q, *J*=7.1 Hz, 2H), 4.19 (q, *J*=7.1 Hz, 2H), 6.09–6.13 (m, 1H), 7.23 (ddd, *J*₁=8.0, *J*₂=4.8, *J*₃=0.6 Hz, 1H), 7.62 (ddd, *J*₁=8.0, *J*₂=2.2, *J*₃=1.7 Hz, 1H), 8.47 (dd, *J*₁=4.7, *J*₂=1.1 Hz, 1H), 8.61 ppm (d, *J*=

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1.8 Hz, 1H); ¹³C NMR (CDCl₃, 300 MHz): δ = 14.1, (s, 2CH₃), 28.4 (s, CH₂), 29.6 (s, CH₂), 40.8 (s, CH), 41.6 (s, CH), 60.8 (s, CH₂), 60.8 (s, CH₂), 123.1 (s, CH), 123.9 (s, CH), 132.3 (s, CH), 132.5 (s, C), 136.2 (s, C), 146.7 (s, CH), 148.4 (s, CH), 174.3 (s, C), 174.4 ppm (s, C); HRMS: *m*/*z*: calcd for C₁₇H₂₂NO₄: 304.1543 [*M*+1]⁺; found: 304.1538.

(*trans*)-Diethyl 4-acetoxymethyl-4-cyclohexene-1,2-dicarboxylate (3n): By following the general procedure described above, 3n (64 mg, 43% yield) was obtained as a yellowish oil by starting from 49 mg of 1j. ¹H NMR (CDCl₃, 300 MHz): δ =1.25 (t, *J*=7.1 Hz, 3H), 1.26 (t, *J*=7.1 Hz, 3H), 2.07 (s, 3H), 2.18–2.28 (m, 2H), 2.36–2.53 (m, 2H), 2.78–2.93 (m, 2H), 4.14 (q, *J*=7.1 Hz, 2H), 4.16 (q, *J*=7.1 Hz, 2H), 4.46 (s, 2H), 5.74–5.75 ppm (m, 1H); ¹³C NMR (CDCl₃, 300 MHz): δ =14.1, (s, 2CH₃), 20.9 (s, CH₃), 27.8 (s, CH₂), 28.6 (s, CH₂), 124.0 (s, CH), 41.3 (s, CH), 60.7 (s, CH₂), 60.7 (s, CH₂), 67.6 (s, CH₂), 124.0 (s, CH), 131.3 (s, C), 170.8 (s, C), 174.4 (s, C), 174.5 ppm (s, C); HRMS: *m/z*: calcd for C₁₅H₂₃O₆: 299.1489 [*M*+1]⁺; found: 299.1492.

(*trans*)-Diethyl 4-methoxycarbonyl-4-cyclohexene-1,2-dicarboxylate (30): By following the general procedure described above, **30** (65 mg, 46% yield) was obtained as a yellowish oil by starting from 42 mg of **1k**. ¹H NMR (CDCl₃, 300 MHz): δ =1.24 (t, *J*=7.1 Hz, 3H), 1.25 (t, *J*=7.1 Hz, 3H), 2.30–2.42 (m, 2H), 2.57–2.68 (m, 1H), 2.74–2.89 (m, 3H), 3.73 (s, 3H), 4.15 (q, *J*=7.1 Hz, 2H), 4.15 (q, *J*=7.1 Hz, 2H), 6.93–6.95 ppm (m, 1H); ¹³C NMR (CDCl₃, 300 MHz): δ =13.9, (s, 2 CH₃), 26.5 (s, CH₂), 28.0 (s, CH₂), 40.2 (s, CH), 40.9 (s, CH), 51.6 (s, CH₃), 60.6 (s, 2 CH₂), 128.3 (s, C), 136.7 (s, CH), 166.4 (s, C), 173.8 (s, C), 173.9 ppm (s, C); HRMS: *m*/*z*: calcd for C₁₄H₂₁O₆: 285.1333 [*M*+1]⁺; found: 285.1327.

(*trans*)-Diethyl 4-(triisopropylsilyl)-4-cyclohexene-1,2-dicarboxylate (3p): By following the general procedure described above, **3p** (44 mg, 31% yield) was obtained as a yellowish oil by starting from 112 mg of **1**. ¹H NMR (CDCl₃, 300 MHz): δ =1.03–1.05 (m, 21 H), 1.25 (t, *J*=7.1 Hz, 3H), 1.25 (t, *J*=7.1 Hz, 3H), 2.14–2.32 (m, 2H), 2.41–2.57 (m, 2H), 2.73–2.90 (m, 2H), 4.14 (q, *J*=7.1 Hz, 2H), 4.15 (q, *J*=7.1 Hz, 2H), 5.94–5.97 ppm (m, 1H); ¹³C NMR (CDCl₃, 300 MHz): δ =14.2 (s, 2CH₃), 17.7 (s, 3CH), 18.7 (s, 6CH₃), 29.7 (s, CH₂), 31.5 (s, CH₂), 41.3 (s, CH), 41.9 (s, CH), 60.5 (s, 2CH₂), 132.3 (s, C), 135.5 (s, CH), 175.0 (s, C), 175.2 ppm (s, C); HRMS: *m/z*: calcd for C₂₁H₃₉O₄Si: 383.2612 [*M*+1]⁺; found: 283.2623.

Dimethyl 1-vinyl-3-cyclohexene-1,4-dicarboxylate (4): By following the general procedure described above, **4** (75 mg, 67% yield) was obtained as a yellowish oil by starting from 42 mg of **1k**. ¹H NMR (CDCl₃, 300 MHz): δ =1.75–1.84 (m, 1 H), 2.03–2.12 (m, 1 H), 2.26–2.39 (m, 3 H), 2.74–2.83 (m, 1 H), 3.67 (s, 3 H), 3.70 (s, 3 H), 5.08 (d, *J*=17.5 Hz, 1 H), 5.14 (d, *J*=10.7 Hz, 1 H), 5.85 (dd, *J*₁=17.4, *J*₂=10.7 Hz, 1 H), 6.92–6.96 ppm (m, 1 H); ¹³C NMR (CDCl₃, 300 MHz): δ =21.7 (s, CH₂), 29.4 (s, CH₂), 32.1 (s, CH₂), 47.2 (s, C), 51.5 (s, CH₃), 52.2 (s, CH₃), 115.2 (s, CH₂), 129.3 (s, C), 137.0 (s, CH), 139.3 (s, CH), 167.3 (s, C), 174.8 ppm (s, C); HRMS: *m/z*: calcd for C₁₂H₁₇O₄: 225.1121 [*M*+1]⁺; found: 225.1110.

(*trans*)-Diethyl 4-[2-(benzylamino)-1,1-difluoro-2-oxoethyl]-4-cyclohexene-1,2-dicarboxylate (6a): By following the general procedures described above, 6a (34 mg, 70% yield) was obtained as a white solid by starting from 25 mg of 5a.^[20] M.p. 61–63 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.24$ (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.23–2.38 (m, 2H), 2.51–2.61 (m, 2H), 2.81–2.95 (m, 2H), 4.14 (q, J = 7.11 Hz, 4H), 4.50 (d, J = 5.8 Hz, 2H), 6.22 (brs, 1H), 6.70 (brs, 1H), 7.27–7.39 ppm (m, 5H); ¹³C NMR (CDCl₃, 300 MHz): $\delta = 14.1 = (s, 2CH_3), 25.0$ (s, CH₂), 27.3 (s, CH₂), 40.3 (s, CH), 40.6 (s, CH), 43.6 (s, CH₂), 60.9 (s, CH₃), 60.9 (s, CH₃), 114.7 (t, ¹*J*(C,F)=251.4 Hz, CF₂), 127.7 (s, CH), 127.8 (s, 2CH), 128.9 (s, 2CH), 128.9 (t, ²*J*(C,F)=24.2 Hz, C), 136.72 (s, C), 163.2 (t, ²*J*(C,F)=30.9 Hz, C), 173.7 (s, C), 173.9 ppm (s, C); ¹⁹F NMR (CDCl₃, 282 MHz): $\delta = -136.4$ (d, *J* (F,F)=258.2 Hz, 1F), -137.5 ppm (d, *J*(F,F)=258.2 Hz, 1F); HRMS (ES⁺): *m/z*: calcd for C₂₁H₂₇F₂NO₅: 410.1774 [*M*+1]⁺; found: 410.1776.

Diethyl 4-[2-(benzylamino)-1,1-difluoro-2-oxoethyl]-1,4-cyclohexadiene-1,2-dicarboxylate (6b): By following the general procedures described above, **6b** (27 mg, 55% yield) was obtained as a dark-brown oil by starting from 25 mg of **5a**. ¹H NMR (CDCl₃, 300 MHz): δ =1.29 (t, *J*=7.2 Hz, 3H), 1.30 (t, *J*=7.2 Hz, 3H), 3.10 (s, 4H), 4.23 (q, *J*=7.2 Hz, 4H), 4.50 (d, *J*=6 Hz, 2H), 6.22 (brs, 1H), 6.70 (brs, 1H), 7.26–7.39 ppm (m, 5H);

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¹³C NMR (CDCl₃, 300 MHz): δ =14.4 (s, CH₃), 14.4 (s, CH₃), 25.7 (t, ³*J*-(C,F)=3.0 Hz, CH₂), 28.5 (s, CH₂), 44.1 (s, CH₂), 61.8 (s, CH₂), 61.9 (s, CH₂), 115.0 (t, ¹*J*(C,F)=251.8 Hz, CF₂), 125.6 (t, ³*J*(C,F)=8.7 Hz, CH), 127.3 (t, ²*J*(C,F)=24.0 Hz, C), 128.3 (s, 2CH), 128.5 (s, CH), 129.4 (s, 2CH), 131.6 (s, C), 131.8 (s, C), 137.1 (s, C), 163.5 (t, ²*J*(C,F)=30.4 Hz, C), 167.5 (s, C), 167.8 ppm (s, C); ¹⁹F NMR (CDCl₃, 282 MHz): δ = -108.6 ppm (s, 2F); HRMS (EI⁺): *m*/*z*: calcd for C₂₁H₂₃F₂NO₅: 407.1544 [*M*]⁺; found: 407.1546.

N-Benzyl-2-(1,3-dioxo-2-phenyl-2,3,3 a,4,7,7 a-hexahydro-1H-isoindol-5-

yl)-2,2-difluoroacetamide (6c): By following the general procedure A described above, **6c** (31 mg, 63 % yield) was obtained as a dark-brown oil by starting from 25 mg of **5a**. ¹H NMR (CDCl₃, 300 MHz): δ =2.32–2.47 (m, 2H), 2.82–2.93 (m, 2H), 3.27–3.38 (m, 2H), 4.46 (d, *J*=5.7 Hz, 2H), 6.49–6.55 (m, 1H), 6.68 (brs, 1H), 7.27–7.47 ppm (m, 10H); ¹³C NMR (CDCl₃, 300 MHz): δ =22.8 (s, CH₂), 23.9 (s, CH₂), 38.7 (s, CH), 39.1 (s, CH), 43.7 (s, CH₂), 114.2 (t, ¹*J*(C,F)=251.0 Hz, CF₂), 126.5 (s, 2CH), 127.9 (s, 2CH), 128.0 (s, CH), 128.7 (s, CH), 128.9 (s, 2CH), 129.1 (s, 2CH), 129.9 (t, ³*J*(C,F)=8.9 Hz, CH), 131.8 (s, C), 131.9 (t, ²*J*(C,F)=24.4 Hz, C), 136.6 (s, C), 162.8 (t, ²*J*(C,F)=30.1 Hz, C), 177.7 (s, C), 178.1 ppm (s, C); ¹⁹F NMR (CDCl₃, 282 MHz): δ =-106.5 ppm (d, *J*_{FF}=258.1 Hz, 1F), -108.7 ppm (d, *J*_{FF}=258.4 Hz, 1F); HRMS (EI⁺): *m/z*: calcd for C₂₃H₂₀F₂N₂O₃: 410.1442 [*M*]⁺; found: 410.1445.

N-Benzyl-2-(9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracen-2-yl)-2,2-difluoroacetamide (6d): By following the general procedures described

fluoroacetamide (6d): By following the general procedures described above, 6d (24 mg, 50% yield) was obtained as a dark-brown oil by starting from 25 mg of 5a. ¹H NMR (CDCl₃, 300 MHz): δ =2.35–2.45 (m, 2H), 2.57–2.70 (m, 2H), 3.37–3.43 (m, 1H), 3.45–3.50 (m, 1H), 4.50 (d, J=5.8 Hz, 2H), 6.23–6.28 (m, 1H), 6.8 (brs, 1H), 7.27–7.38 (m, 5H), 7.73–7.79 (m, 2H), 7.99–8.07 ppm (m, 2H); ¹³C NMR (CDCl₃, 300 MHz): δ =22.0 (s, CH₂), 24.3 (s, CH₂), 43.6 (s, CH₂), 45.6 (s, CH), 45.8 (s, CH), 114.6 (t, ¹J(C,F)=250.9 Hz, CF₂), 126.9 (CH), 127.0 (CH), 127.4 (t, ³J-(C,F)=8.6 Hz, CH), 127.8 (CH), 127.9 (CH), 128.6 (t, ²J(C,F)=29.2 Hz, C), 128.8 (CH), 133.6 (C), 133.7 (C), 134.6 (CH), 136.1 (C), 163.1 (t, ²J-(C,F)=30.6 Hz, C), 197.0 (s, C); 197.1 ppm (s, C); ¹⁹F NMR (CDCl₃, 282 MHz): δ =-107.5 ppm (s, 2F); HRMS (ES⁺): *m*/*z*: calcd for C₂₃H₂₀F₂NO₃: 396.1406 [*M*+1]⁺; found: 396.1404.

(trans)-Diethyl 4-{1,1-difluoro-2-oxo-2-[(S)-1-phenylethylamino]ethyl}-4cyclohexene-1,2-dicarboxylate (6e+6e'): By following the general procedures described above, 6e+6e' (37 mg, 73% yield) were obtained as a dark-brown oil by starting from 27 mg of 5b.^[20] ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.23$ (t, J = 7.2 Hz, 6 H), 1.54 (d, J = 6.9 Hz, 3 H), 2.20–2.31 (m, 2H), 2.52- 2.58 (m, 2H), 2.79–2.92 (m, 2H), 4.13 (q, J=7.2 Hz, 4H), 5.08-5.18 (m, 1H), 6.17 (brs, 1H), 6.64 (d, J=6.64 Hz, 1H), 7.27-7.39 ppm (m, 5H); ¹³C NMR (CDCl₃, 300 MHz): $\delta = 14.1$ (CH₃), 21.3 (2 CH₃), 24.9 (CH₂), 27.2 (CH₂), 40.3 (CH), 40.6 (CH), 49.2 (CH), 60.8 (CH₂), 60.9 (CH₂), 114.6 (t, ${}^{1}J(C,F) = 251.7$ Hz, CF₂), 126.1 (2CH), 127.8 (CH), 127.8 (t, ${}^{3}J(C,F) = 8.7$ Hz, CH), 128.8 (2 CH), 128.9 (t, ${}^{2}J(C,F) =$ 24.0 Hz, C), 141.7 (C), 162.3 (t, ${}^{2}J(C,F) = 30.5$ Hz, C), 173.7 (C), 173.8 ppm (C); ¹⁹F NMR (CDCl₃, 282 MHz): $\delta = -106.7$ (d, J(F,F) =258.7 Hz, 1F), -106.8 (d, J(F,F)=258.1 Hz, 1F), -107.9 (d, J(F,F)= 258.9 Hz, 1F), -107.9 ppm (d, J(F,F)=258.7 Hz, 1F); HRMS (ES⁺): m/ z: calcd for C₂₂H₂₈F₂NO₅: 424.1936 [*M*+1]⁺; found: 424.1940.

2-(1,3-Dioxo-2-phenyl-2,3,3 a,4,7,7 a-hexahydro-1*H*-isoindol-5-yl)-2,2-difluoro-N-[(S)-1-phenylethyl]acetamide (6 f+6 f'): By following the general procedures described above, 6f+6f' (36 mg, 70% yield) were obtained as a dark-brown solid by starting from 27 mg of 5b. M.p. 113-115°C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.53$ (d, J = 6.9 Hz, 3H), 2.31– 2.46 (m, 2H), 2.76-2.91 (m, 2H), 3.25-3.36 (m, 2H), 5.04-5.16 (m, 1H), 6.45–6.51 (m, 1H), 6.65 (brs, 1H), 7.22–7.48 ppm (m, 10H); $^{\rm 13}{\rm C}\,{\rm NMR}$ $(CDCl_3, 300 \text{ MHz}): \delta = 21.1 (CH_3), 21.3 (CH_3), 22.7 (CH_2), 23.8 (CH_2),$ 38.7 (CH), 39.0 (CH), 49.2 (CH), 49.3 (CH), 114.0 (t, ¹J(C,F)=251.6 Hz, CF₂), 114.1 (t, ¹*J*(C,F)=252 Hz, CF₂), 126.1 (2 CH), 126.2 (2 CH), 126.4 (2CH), 126.5 (2CH), 127.7 (CH), 127.8 (CH), 128.6 (CH), 128.7 (CH), 128.8 (2 CH), 129.1 (2 CH), 129.8 (t, ³J(C,F)=8.7 Hz, CH), 129.8 (t, ³J- $(C,F) = 8.8 \text{ Hz}, CH), 131.7 (C), 131.8 (C), 131.8 (t, {}^{2}J(C,F) = 24.6 \text{ Hz}, C),$ 131.9 (t, ${}^{2}J(C,F) = 24.6$ Hz, C), 141.5 (C), 141.7 (C), 161.9 (t, ${}^{2}J(C,F) =$ 30 Hz, C), 177.7 (C), 177.8 (C), 178.1 (C), 178.2 ppm (C); ¹⁹F NMR (CDCl₃, 282 MHz): $\delta = -105.9$ (d, J(F,F) = 259.7 Hz, 1F), -106.4 (d, J-

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(F,F) = 257.6 Hz, 1F), -108.6 (d, J(F,F) = 259.7 Hz, 1F), -108.8 ppm (d, J(F,F) = 257.6 Hz, 1F); HRMS (EI⁺): <math>m/z calcd for $C_{24}H_{22}F_2N_2O_3$: 424.1598 $[M]^+$; found: 424.1599.

(R)-Diethyl 4-[1,1-difluoro-2-oxo-2-(1-phenylethylamino)ethyl]ciclohexa-1,4-diene-1,2-dicarboxylate (6g): By following the general procedures described above, 6g (30 mg, 60 % yield) was obtained as a dark-brown oil by starting from 27 mg of **5b**. $[\alpha]_{25}^{D} = -88.9$ (c = 1.0 in CHCl₃); ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.29$ (t, J = 7.2 Hz, 6H), 1.56 (d, J = 6.9 Hz, 3H), 3.12 (s, 4H), 4.23 (q, J=7.2 Hz, 4H), 5.14 (quint, J=7.2 Hz, 1H), 6.17-6.19 (m, 1H), 6.58 (brs, 1H), 7.29–7.39 ppm (m, 5H); ¹³C NMR (CDCl₃, 300 MHz): $\delta = 14.4$ (s, CH₃), 14.4 (s, CH₃), 21.8 (s, CH₃), 25.7 (t, ${}^{4}J(C,F) =$ 2.6 Hz, CH₂), 28.5 (s, CH₂), 49.7 (s, CH), 61.8 (s, CH₂), 62.4 (s, CH₂), 114.9 (t, ${}^{1}J(C,F) = 251.6$ Hz, CF₂), 125.6 (t, ${}^{3}J(C,F) = 8.7$ Hz, CH), 126.6 (s, 2 CH), 127.3 (t, ²*J*(C,F)=24.2 Hz, C), 128.3 (s, CH), 129.3 (s, 2 CH), 131.6 (s, C), 131.8 (s, C), 142.1 (s, C), 162.6 (t, ${}^{3}J(C,F) = 30.4$ Hz, C), 167.5 (s, C), 167.8 ppm (s, C); ¹⁹F NMR (CDCl₃, 282 MHz): $\delta = -106.8$ (d, J-(F,F)=258.7 Hz, 1F), -106.9 (d, J(F,F)=258.6 Hz, 1F), -107.9 (d, J-(F,F)=258.6 Hz, 1F), -108.0 ppm (d, J (F,F)=258.7 Hz, 1F); HRMS (EI⁺): m/z: calcd for C₂₂H₂₆F₂NO₅: 422.1774 [*M*+1]⁺; found: 422.1753.

Diethyl 4-(1,1-difluoro-2-oxo-2-phenylethyl)-1,4-cyclohexadiene-1,2-dicarboxylate (6h): By following the general procedures described above, **6h** (25 mg, 55 % yield) was obtained as a dark-brown oil by starting from 22 mg of **5c**^[20]. ¹H NMR (CDCl₃, 300 MHz): δ =1.23 (t, *J*=7.2 Hz, 3H), 1.24 (t, *J*=7.2 Hz, 3H), 3.16 (s, 4H), 4.17 (q, *J*=7.2 Hz, 2H), 4.17 (q, *J*=7.2 Hz, 2H), 6.19–6.20 (brm, 1H), 7.47 (dd, *J*₁=*J*₂=6 Hz, 2H), 7.63 (tt, *J*₁=7.2 Hz, *J*₂=1.5 Hz, 1H), 8.03 ppm (d, *J*=7.2 Hz, 2H); ¹³C NMR (CDCl₃, 300 MHz): δ =13.9 (s, CH₃), 14.0 (s, CH₃), 25.3 (t, ⁴*J*(C,F)=2.8 Hz, CH₂), 28.1 (s, CH₂), 61.4 (s, CH₂), 61.5 (s, CH₂), 116.3 (t, ¹*J*-(C,F)=251.9 Hz, CF₂), 125.7 (t, ³*J*(C,F)=8.6 Hz, CH), 128.0 (t, ²*J*(C,F)=23.8 Hz, C), 128.7 (s, 2CH), 130.2 (t, ⁴*J*(C,F)=2.9 Hz, 2CH), 131.2 (s, C), 188.5 ppm (t, ²*J*(C,F)=30.6 Hz, C); ¹⁹F NMR (CDCl₃, 282 MHz): δ =-103.2 ppm (s, 2F); HRMS (EI⁺): *m*/*z*: calcd for C₂₀H₂₀F₂O₅: 378.1269 [*M*]⁺; found: 378.1279.

(*trans*)-Diethyl **4-[1,1-difluoro-2-oxo-2-(phenylamino)ethyl]-4-cyclohexene-1,2-dicarboxylate (6i):** By following the general procedures described above, **6i** (32 mg, 70% yield) was obtained as a yellow oil by starting from 22 mg of **5c**. ¹H NMR (CDCl₃, 300 MHz): δ =1.24 (t, *J*=7.2 Hz, 3H), 1.25 (t, *J*=7.2 Hz, 3H), 2.23–2.41 (m, 2H), 2.51–2.64 (m, 2H), 2.84–2.98 (m, 2H), 4.14 (q, *J*=7.2 Hz, 4H), 6.17–6.22 (m, 1H), 7.48 (dd, *J*₁=*J*₂=7.8 Hz, 2H), 7.63 (tt, *J*₁=7.2, *J*₂=1.5 Hz, 1H), 8.03 ppm (d, *J*=7.2 Hz, 2H); ¹³C NMR (CDCl₃, 300 MHz): δ =14.1 (s, 2CH₃), 25.0 (s, CH₂), 27.3 (s, CH₂), 40.4 (s, CH), 40.6 (s, CH), 60.9 (s, CH₂), 61.0 (s, CH₂), 116.4 (t, ^{*I*}/₂(C,F)=24.2 Hz, C), 130.1 (t, ⁴/₂(C,F)=2.27 Hz, 2CH), 132.2 (s, C), 134.4 (s, CH), 173.7 (s, C), 173.9 (s, C), 188.8 ppm (t, ²/₂(C,F)=31.0 Hz, C); ¹⁹F NMR (CDCl₃, 282 MHz): δ =-111.7 (d, *J*-(F,F)=272.2 Hz, 1F), -112.8 ppm (d, *J*(F,F)=272.2 Hz, 1F); HRMS (EI⁺): *m/z*: calcd for C₂₀H₂₃F₂O₅: 381.1508 [*M*+1]⁺; found: 381.1514.

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CHEMISTRY

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Relay Metathesis -

S. Fustero,* P. Bello, J. Miró, A. Simón, C. del Pozo*.....

1,7-Octadiene-Assisted Tandem Multicomponent Cross-Enyne Metathesis (CEYM)-Diels-Alder Reactions: A Useful Alternative to Mori's Conditions



Ruthenium catalysis: A new, multicomponent, tandem cross-enyne metathesis (CEYM)-Diels–Alder reaction that is mediated by 1,7-octadiene is described. The ethylene liberated in the ring-closing metathesis of this diene initiates the enyne metathesis and, in the presence of a dienophile, the tandem process takes place in an efficient manner (see scheme).