H-bond Controlled *anti*-aza-Michael Addition: Diastereoselective Synthesis of Cyclobutene-containing Amino Acid Derivatives.

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Dedicated to Professor Agustín Arévalo Medina on the occasion of his obituary

Abstract: The chemical reactivity encoded in a highly substituted cyclobutanic platform based on the (*E,E*)-dimethyl 2,2'-(cyclobutane-1,2-diylidene)diacetate structural motive has been explored. The platform features a global C₂-symmetry supported by a dense and interconnected ring functionalization pattern defined by two allylic/benzylic stereogenic oxygen-containing quaternary centers with a 1,2-*trans* configuration and two exocyclic acrylate chains. The reactivity profile is defined by two important kinetic barriers (steric strain and *anti*-aromaticity) and by two structure-biased chemical process: 1) the thermally-driven [3,3]-sigmatropic rearrangement between one of the two equivalent aryloates and the corresponding allylic acrylate chain, and 2) the allylic nucleophilic substitution (S_N2' reaction) involving a tertiary aryloate and its exocyclic double bond (*anti*-Michael addition). The reaction of the platform **3a** (aryl = phenyl) with secondary amines delivered the corresponding cyclobutenic amino acid derivatives **15a-f** in excellent yield (up to ≥95%) and diastereoselectivity (up to 99:1). Computational studies are described to rationalize the observed diastereoselectivity.

Introduction

In the realm of the carbon-carbon and carbon-heteroatom bond forming reactions, the Michael addition (i.e., the conjugated addition of a nucleophile onto an α,β-unsaturated acceptor) occupies a relevant place.^[1] The reaction tolerates a vast array of nucleophiles and acceptors combinations to selectively create a new bond at the β-position of the unsaturated acceptor. The difference in the value of the LUMO's orbital coefficients of the two sp²-carbon atoms of the conjugated double bond biases the

addition of the nucleophile on the unsaturated system. Normally, the polarization of the conjugated double bond directs the reactivity of the system toward the β-position. However, in certain cases, the polarization of the system can be reversed and the attack on the α-position dominates the outcome of the reaction. The reaction is designated as an *anti*-Michael^[2] addition to highlight this reversed outcome. Although not as common as the Michael addition, a good number of examples have been reported in the recent chemical literature.^[3] A paradigmatic example of this unusual reactivity pattern is the α-addition to alkyl propiolates catalyzed by tertiary phosphines (Scheme 1A).^[4] The formation of a vinyl phosphonium intermediate reverses the initial polarization of the triple bond and allows the nucleophilic addition on the α-position to the ester group. Sulphone,^[5] trifluoromethyl,^[6] electron-deficient aromatic^[7] or nitro^[8] groups at the β-position of the α,β-unsaturated system have shown to have the same biasing effect (directing groups) (Scheme 1B). α-Addition has been also accomplished by other methods^[3] including the use of palladium complexes, organometallic reagents or strong bases. In more complex systems, the inherent 1,4-reactivity of α,β-unsaturated esters can be diverted toward the α-addition model by stereoelectronic factors imposed by the rest of the molecule. This resulted to be the case of the fully substituted cyclobutanic platforms **3**^[9] (Scheme 2A), incorporating two exocyclic α,β-unsaturated ester functionalities (acrylates) bearing a tertiary (benzylic) aryloate group at the allylic position. The high

a) α-Addition to alkyl propiolates catalyzed by tertiary phosphines

a = Michael addition; b = *anti*-Michael addition

b) α-Addition to α,β-unsaturated carbonyls biased by a directing group

Scheme 1. A) Phosphine catalyzed α-addition to propiolates. B) Reversing the normal 1,4-addition mode by using directing groups. DG = Directing group. EWG = electron-withdrawing group.

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functional density on the four-membered ring defines a particular reactivity profile for the whole platform which is triggered by a diastereoselective *anti*-Michael addition on one of the two unsaturated system.

Results and Discussion

Within a wide research program aimed to map biological activity in the chemical space using the small molecule approach,^[10] we have been interested in the design and synthesis of densely functionalized small chemical platforms featuring a pluripotent reactivity profile.^[11] We have already shown how this concept can be incorporated and efficiently instrumentalized in diversity-oriented synthetic (DOS) programs aimed to transform simple and linear structures (propargyl vinyl ethers^[12] or tertiary skipped diynes^[13]) into an array of topological (skeletal) diverse structures.^[14] In this line of thought, the cyclobutanic structures **3** were envisioned as potential pluripotent platforms for DOS because: 1) they feature a dense and interconnected ring functionalization pattern defined by two allylic/benzylic stereogenic oxygen-containing quaternary centers with a 1,2-*trans* configuration; 2) they present a C₂ axis of symmetry, and 3) they are easily assembled^[9] from the appropriate alkyl propiolates **1** and the corresponding aromatic

a) Multicomponent synthesis from alkyl propiolates and 1,2-diketones

b) Hypothesized reactivity profiles encoded into these platforms

Scheme 2. Multicomponent synthesis and hypothesized reactivity profile encoded on cyclobutanes **3**.

1,2-diketones **2** through a highly stereoselective Et₃N-catalyzed ABB' 3-component reaction^[15] (modular assembling) (Scheme 2A). The presence of the two quaternary allylic esters defines a convenient scenario for the development of chemical processes launched by thermally-driven [3,3]-sigmatropic rearrangements (Scheme 2B), which would transfer the chiral information from the ring (quaternary stereogenic centers) to the acrylate chains. In addition to this reactivity profile, the allylic/benzylic nature of each one of the otherwise identical quaternary centers and the C₂ symmetry of the ring would favor the formation of stabilized tertiary carbocations (neighboring group participation, bicyclic structure) and a net polarization change in the reactivity of the conjugated double bonds (*anti*-Michael addition). Whereas the first reactivity principle should be controlled by the symmetry of the orbitals participating in the event, the second one should be governed by the bicyclic geometry of the stabilized tertiary carbocation. With these ideas as guides, we undertook the study of the reactivity principles encoded in these platforms and their application to the small molecule approach to the drug/probe discovery.

We began this work by studying the thermal reactivity of these platforms. With this idea, cyclobutene **3a** (Ar = Ph; R = Me) was dissolved in toluene and submitted to microwave irradiation (190 °C, 200 W) in a closed vessel (Scheme 3). After 1 h of irradiation, the reaction was quenched to give the all-C_{sp2} cyclobutanic platform **7** (18% yield; *E,Z/E,E*: 95:5) along with a mixture of other unidentified compounds. The final placement of a benzoate unit at the α-position of the acetate chain confirmed that the expected [3,3]-sigmatropic rearrangement had taken place under these conditions to give the rearranged intermediate **4** (Scheme 3). The subsequent elimination of the tertiary benzoate would afford the final product **7** which would have lost all the chiral information encoded in the original molecule. When the reaction was carried out in the presence of a drop of Et₃N as a basic additive, the yield of cyclobutanic compound **7** increased up to 70% but the isomeric ratio decreased to 75:25 as a consequence of acid-base equilibrations of the reaction intermediates.

Scheme 3. Microwave-assisted rearrangement of **3a** to all-C_{sp2} platform **7**.

Interestingly, the hydrogenation of **3a** afforded cyclobutene **8** in quantitative yield (Scheme 4). It is remarkable that the

internal double bond had resisted a further hydrogenation under these reductive conditions. This unexpected stability can be ascribed to the steric strain that four C_{sp3} and a high degree of

Scheme 4. Base-assisted rearrangement of **8** to all-C_{sp2} platform **10**.

substitution would introduce into the ring. It would be very interesting to know if this strain-controlled ring reactivity is also operative in other fully substituted cyclobutenes.^[16] The treatment of cyclobutene **8** with NaOMe in MeOH afforded the all-C_{sp2} cyclobutene compound **10** by two consecutive base-assisted allylic eliminations.

The reactivity of the platform **3a** was assayed against strong bases and acids (Scheme 5). The treatment with KOH in MeOH at room temperature generated the all-C_{sp2} cyclobutene **11** in 92 % yield as a mixture of isomers (*E,Z/E,E* = 63:37). Because the thermally-assisted [3,3]-sigmatropic rearrangement could not be performed at room temperature, the platform reacted through a tandem nucleophile-driven allylic substitution-base-promoted allylic elimination process. While the initial reaction is facilitated by the allylic/benzylic nature of the benzoate leaving group, the subsequent allylic elimination is favoured by the presence of the previously introduced OMe group at the acetate chain. On the other hand, the acid treatment (trifluoroacetic acid) of the platform **3a** generated the mono hydroxylated derivative **12** (detected by ¹H-NMR of the reaction residue) which was subsequently converted into the 2-hexendioate derivative **13** by overnight treatment with triethylamine. The observed ring-opening reaction is allowed because the C-C bond breaking generates a stabilized enolate anion and a neutral and stable conjugated ketone and a fully substituted olefin. The resulting product **13** represents a nice example of a densely functionalized platform with all its reactive functionalities chemically differentiated for selective chemical handling (benzoyl/enol benzoate; acetate/acrylate chain).

With these results at hand, we next explored the reactivity of this platform toward neutral nucleophiles (Scheme 6). The platform did not react with methanol at room temperature, even when it was used as solvent. Surprisingly, the reaction with phenylmethanethiol afforded the isomerized product **14** in a 78% yield. This result was not easily explained according to the previous established results and we do not have a consistent explanation for it. The reaction with secondary aliphatic amines afforded the corresponding amino acid derivatives **15**

Scheme 5. Reactivity of platform **3a** toward strong bases and acids.

with high efficiency and elevated diastereoselection even under temperatures as high as 60 °C (Table 1). A survey of secondary amines reacted with **3a** to afford the corresponding cyclobutene-containing amino acid derivatives **15a-f** with an excellent average yield (93%) and an impressive diastereoselectivity (up to 99:1). In terms of diastereoselectivity, the lowest ratios were featured by the less sterically demanding and more reactive cyclic amines (Table 1, entries 6 and 7). The importance of the nucleophilic strength of the amine was highlighted by the absence of reaction when aromatic amines or amides were used as the nucleophiles.

Scheme 6. Reactivity of platform **3a** toward secondary amines. Diastereoselective synthesis of cyclobutenic α -amino esters **15**.

Table 1. Diastereoselective addition of secondary amines on cyclobutane **3a**.

Entry	R ¹ ,R ²	time	T	Yield (%)	dr
1	Allyl,Allyl	a 16 h	r.t.	≥95	98:2
2	Allyl,Allyl	a 3 h	60 °C	83	94:6
3	Me,Bn	b 2 h	r.t.	≥95	95:5
4	Bn,Bn	c 16 h	60 °C	≥95	99:1
5	PMBn,PMBn ^[a]	d 16 h	60 °C	≥95	98:2
6	Pyrrolidine	e 24 h	r.t.	≥95	89:11 ^[b]
7	Morpholine	f 24 h	r.t.	93	92:8

[a] PMBn = *p*-Methoxybenzyl. [b] 1:1 after flash chromatography.

The stereochemistry of the new stereogenic centre was determined by X-ray diffraction analysis of the derivative **15f**^[17]

(Figure 1). The observed stereochemical pattern indicates that the addition of the nucleophile has taken place *by the same face* to the benzoate leaving group (Scheme 6). This stereochemical outcome would be that expected from a $\text{S}_{\text{N}}1'$ process involving a stabilized tertiary carbocation such it is outlined in the Scheme 2B. On the other hand, the observed dependence of the platform reactivity with the nucleophile strength does not fit well with a $\text{S}_{\text{N}}1'$ process in which the nucleophile nature should play a less relevant role than the carbocation stability (this is inherent to the platform and it is the same for all the nucleophiles). This reliance is more in accordance with an allylic substitution process (*anti-aza-Michael addition*) in which the nucleophile addition step is the rate determining step of the process. With regard to the origin of the observed selectivity toward the nucleophile's approach by the β -face of the double bond, we hypothesized that it could be related to the development of a stabilizing $\text{NH}\cdots\text{O}=\text{C}$ interaction between the incoming amine and the benzoate leaving group. It has to be noted that this secondary interaction cannot be established in the corresponding α -face attack and consequently, the transition state for this addition would be higher in energy than that for the β -face attack. This expected energetic difference between the two possible transition states should be enough to selectively funnel the process toward the kinetic formation of the observed product.

Figure 1. X-ray structure of amino derivative **15f**.

To prove the feasibility of this hypothesis, Density Functional Theory (DFT) calculations were carried out at the dispersion corrected $\text{PCM}(\text{CH}_2\text{Cl}_2)\text{-B3LYP-D3/6-31G(d)}$ level.^[18] To this end, the reaction profiles for the reaction of model cyclobutane **3M**, where the benzoate groups were replaced by acetate groups, and dimethylamine leading to diastereoisomers **15M** were computed (Figure 2).

Two possible initial reactant complexes can be formed upon addition of NHMe_2 to **3M**, namely **INT1-A**, where the nucleophile approaches **3M** by the β -face of the double bond, and **INT1-B**, where the approach takes place from the opposite face, i.e., from the opposite place to the adjacent acetate group. Our calculations indicate that **INT1-A** lies 3.4 kcal/mol below **INT1-B**, which can be mainly ascribed to the occurrence of a stabilizing intermolecular $\text{NH}\cdots\text{O}=\text{C}$ hydrogen bond in **INT1-A** that is not present in **INT1-B**. This interaction approximates the reactive centres (i.e., the lone-pair of the nitrogen atom of

NHMe_2 and the carbon atom of the double bond of **3M**) and as a result, the corresponding nucleophilic attack via the transition state **TSA** proceeds with a lower activation barrier ($\Delta E^\ddagger = 6.7$ 8.5

Conclusions

We have studied the chemical reactivity encoded in the highly substituted cyclobutanic platform **3** incorporating the (*E,E*)-dimethyl 2,2'-(cyclobutane-1,2-diylidene)diacetate motive. We have found that the reactivity profile for these platforms is defined by: 1) a high kinetic barrier to the formation of an all- C_{sp^3} cyclobutane ring (steric strain); 2) a high kinetic barrier for all processes involving a cyclobutadiene intermediate (*anti*-aromaticity); 3) a favoured allylic nucleophilic substitution involving a tertiary aryloate group and its allylic acrylate chain (*anti*-Michael addition). The stereochemical outcome of the observed *anti*-aza-Michael reaction with secondary amines is controlled by the formation of an $\text{NH}\cdots\text{O}=\text{C}$ interaction between the amine and the carbonyl group of the aryloate leaving group, which is present along the entire reaction coordinate. This stabilizing secondary interaction biases the nucleophile attack of the secondary amine on the same face of the aryloate leaving group to afford the corresponding cyclobutanic amino acid derivatives in excellent yields (up to $\geq 95\%$) and diastereoselectivity (up to 99:1). Computational studies rationalize the observed diastereoselectivity and support the stereochemical model.

Experimental Section

General Remarks: ^1H NMR and ^{13}C NMR spectra of CDCl_3 solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz, respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor. FT-IR spectra were measured in chloroform solutions using a FT-IR spectrophotometer. Mass spectra (low resolution) (EI/CI) and HRMS (EI/TOF) were obtained with a gas chromatograph/mass spectrometer. Analytical thin-layer chromatography plates used UV-active silica on aluminum. Melting points (uncorrected) were measured with a Büchi melting Point B-450 apparatus. Flash column chromatography was carried out with silica gel of particle size less than 0.020 mm, using appropriate mixtures of ethyl acetate and hexanes as eluents. All reactions were performed in oven-dried glassware. All materials were obtained from commercial suppliers and used as received unless otherwise noted.

Microwave-assisted rearrangement of 3a. 0.25 mmol of **3a** (147.2 mg) were placed in a microwave glass vessel. 1 mL of toluene and 1 drop of Et_3N were added before the mixture was heated to 190°C for 1 h (200W) in a CEM Discover microwave reactor. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, *n*-hexane/ EtOAc 90/10) to yield **7** (70%).

(E)-2-methoxy-1-((E)-4-(2-methoxy-2-oxoethylidene)-2,3-diphenylcyclobut-2-enylidene)-2-oxoethyl benzoate (7): pale yellow oil; major isomer as drawn, confirmed by NOE experiments (not shown) ^1H NMR (400 MHz, CDCl_3): δ 3.25 (s, 3H), 3.26 (s, 3H), 5.68 (s, 1H), 7.33-7.51 (m, 10H), 7.59-7.63 (m, 3H), 8.14-8.16 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 51.1, 51.8, 110.5, 126.4, 127.4 (2C), 128.48 (2C), 128.54 (2C), 128.7 (2C), 129.1 (2C), 129.4, 129.5, 129.6, 130.1 (2C),

Figure 2. Computed reaction profile for the reaction between model cyclobutane **3M** and NHMe_2 . Bond distances are given in angstroms, while relative energies (free energies, in parenthesis) are given in kcal/mol. All data have been computed at the $\text{PCM}(\text{CH}_2\text{Cl}_2)\text{-B3LYP-D3/6-31G(d)}$ level.

131.4, 133.5, 134.0, 135.3, 142.6, 148.9, 158.7, 161.3, 165.0, 165.3 ppm; MS (70 eV): m/z (%): 466 (M^+ , 59), 435 (6.8), 330 (16), 106 (45), 105 (100), 77 (97) HRMS calculated for $\text{C}_{29}\text{H}_{22}\text{O}_6$: 466.1416, found 466.1396.

Hydrogenation of 3a: 1.0 mmol of **3a** (588.6 mg) was dissolved in EtOAc. 10% Pd(C) was added and the reaction was stirred at room temperature overnight under a hydrogen atmosphere. After filtrating over celite the solvent was removed under reduced pressure. This was followed by isolation of the desired product **8** by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc) 100% yield.

(±)-3,4-bis(2-methoxy-2-oxoethyl)-1,2-diphenylcyclobut-3-ene-1,2-diyl dibenzoate (8): white solid; m.p. 137–139 °C. ^1H NMR (400 MHz, CDCl_3): δ 3.56 (s, 6H), 3.76 (s, 4H), 7.20–7.24 (m, 8H), 7.42–7.46 (m, 12H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 33.1 (2C), 52.0 (2C), 89.9 (2C), 126.3 (4C), 127.8 (2C), 128.1 (4C), 128.5 (4C), 129.5 (4C), 129.8 (2C), 132.9 (2C), 138.0 (2C), 144.0 (2C), 164.9 (2C), 170.0 (2C) ppm; IR (CHCl_3): ν = 3014.8, 1735.0, 1601.8, 1494.8, 1451.0, 1402.5, 1354.1, 1315.8, 1273.1, 1111.9 cm^{-1} ; MS (70 eV): m/z (%): 590 (M^+ , 1.7), 485 (51), 364 (83), 303 (13), 215 (5.3), 105 (100), 77 (99); elemental analysis calcd (%) for $\text{C}_{36}\text{H}_{30}\text{O}_8$: C 73.21; H 5.12; found: C 73.14; H 5.43.

Reaction of 8 with NaOMe/MeOH: 0.25 mmol of **8** (147.7 mg) were dissolved in 2 mL of MeOH and 5 mol eq. of NaOMe were added to the solution. The mixture was allowed to react at RT for 1h before it was quenched with dilute HCl. Extraction with dichloromethane, removal of the solvent and isolation of the desired product by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc) afforded **10** as a mixture of isomers (85:15) in 86% yield.

(2Z,2'E)-dimethyl 2,2'-(3,4-diphenylcyclobut-3-ene-1,2-diylidene)diacetate (10): white solid; m.p. 130–132 °C. ^1H NMR (400 MHz, CDCl_3): δ 3.35 (s, 3H), 3.78 (s, 3H), 5.96 (s, 1H), 6.95 (s, 1H), 7.30–7.36 (m, 5H), 7.37–7.39 (m, 5H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 50.8, 51.5, 103.5, 108.3, 127.7 (2C), 127.85 (2C), 127.92 (2C), 128.8 (2C), 129.0, 129.9, 130.0, 132.5, 150.8, 155.0, 155.3, 158.1, 166.3 (2C) ppm; MS (70 eV): m/z (%): 346 (M^+ , 100), 315 (19), 287 (32), 255 (25), 226 (36), 215 (19), 105 (11); HRMS calculated for $\text{C}_{22}\text{H}_{18}\text{O}_4$: 346.1205, found 346.1193. Characteristic signals for the (Z,Z)-isomer: ^1H NMR (400 MHz, CDCl_3): δ 3.73 (s, 6H), 5.93 (s, 2H).

Reaction of 3a with NaOMe/MeOH: 0.358 mmol of **3a** (210.0 mg) were dissolved in 3 mL of CH_2Cl_2 and 3 mL of 3% KOH/MeOH were added at 0°C. The mixture was allowed to react 2h before it was quenched with dilute HCl. Extraction with dichloromethane, removal of the solvent and isolation of the desired product by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc) afforded **11** as a mixture of isomers in 92% yield.

(Z)-methyl 2-methoxy-2-((E)-4-(2-methoxy-2-oxoethylidene)-2,3-diphenylcyclobut-2-enylidene)acetate and (E)-methyl 2-methoxy-2-((E)-4-(2-methoxy-2-oxoethylidene)-2,3-diphenylcyclobut-2-enylidene)acetate (11): white solid; (major isomer) ^1H NMR (400 MHz, CDCl_3): δ 3.30 (s, 3H), 3.36 (s, 3H), 3.89 (s, 3H), 6.63 (s, 1H), 7.16–7.45 (m, 10H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 50.8, 52.0, 61.2, 107.1, 127.82 (2C), 127.87 (2C), 127.99 (2C), 128.7, 128.96 (2C), 129.3, 130.3, 132.4, 133.4, 139.8, 149.1, 154.5, 155.9, 164.3, 166.5 ppm; (minor isomer) ^1H NMR (400 MHz, CDCl_3): δ 3.24 (s, 3H), 3.39 (s, 3H), 3.77 (s, 3H), 6.27 (s, 1H), 7.16–7.45 (m, 10H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 50.9, 51.0, 60.5, 105.6, 127.5 (2C), 127.76 (2C), 127.92, 128.38 (2C), 128.64 (2C), 131.6, 132.0, 133.8, 138.0, 150.9, 153.8, 155.9, 163.2, 166.3 ppm; IR (CHCl_3): ν = 3014.7, 1713.8, 1436.5, 1280.3, 1222.2 cm^{-1} ; MS (70 eV): m/z (%): 376 (M^+ , 100), 215 (59), 213 (46), 202 (29), 129

(17), 105 (18), 59 (21); elemental analysis calcd (%) for $C_{23}H_{20}O_5$: C 70.57; H 5.92; found: C 70.33; H 6.28.

Reaction of 3a with TFA followed by Et_3N : 0.50 mmol of **3a** (294.3 mg) were dissolved in 2 mL of CH_2Cl_2 and 2 mL of TFA. The mixture was stirred overnight and it was then quenched with saturated $NaHCO_3$ solution. After extraction with dichloromethane, the crude products were stirred overnight with 2.0 mmol of Et_3N . Removal of the solvent and isolation of the desired product by flash column chromatography (silica gel, appropriate mixtures of n-hexane/ $EtOAc$) afforded **13** in 49% yield.

(2Z,4Z)-dimethyl 3-benzoyl-4-(benzoyloxy(phenyl)methylene)hex-2-enedioate (13): 1H NMR (400 MHz, $CDCl_3$): δ 3.48 (s, 3H), 3.49 (s, 2H), 3.78 (s, 3H), 6.20 (s, 1H), 7.20-7.32 (m, 7H), 7.35-7.40 (m, 1H), 7.45-7.51 (m, 3H), 7.60-7.62 (m, 2H), 7.79-7.81 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.1, 51.6, 52.3, 119.3, 120.7, 128.1 (2C), 128.2 (2C), 128.3, 128.4 (2C), 128.6 (2C), 128.8 (2C), 129.6, 130.0 (2C), 132.9, 133.5, 134.7, 136.0, 152.3, 152.5, 163.3, 165.2, 171.0, 195.0 ppm; MS (70 eV): m/z (%): 484 (M^+ , 22), 362 (3.5), 319 (2.9), 105 (100), 77 (65); HRMS calculated for $C_{29}H_{24}O_7$: 484.1522, found 484.1529.

Isomerization of 3a in the presence of $PhCH_2SH$: 0.125 mmol of **3a** (73.6 mg) were dissolved in CH_2Cl_2 . 0.125 mmol of $PhCH_2SH$ were added and the reaction was stirred at room temperature overnight allowing the solvent to evaporate. The desired product **14** was isolated by flash column chromatography (silica gel, appropriate mixtures of n-hexane/ $EtOAc$) 78% yield.

(±)-(3E,4Z)-3,4-bis(2-methoxy-2-oxoethylidene)-1,2-diphenylcyclobutane-1,2-diyl dibenzoate (14): white solid; m.p. 202–204 °C. 1H NMR (400 MHz, $CDCl_3$): δ 3.33 (s, 3H), 3.86 (s, 3H), 7.12-7.22 (m, 8H), 7.27-7.31 (m, 2H), 7.39-7.41 (m, 3H), 7.50-7.57 (m, 4H), 7.66-7.70 (m, 2H), 7.76-7.80 (m, 2H), 7.91 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.3, 52.0, 90.2, 90.9, 125.4, 126.0, 126.8 (2C), 127.8 (2C), 127.9 (2C), 128.04, 128.07 (2C), 128.09 (2C), 128.35, 128.38 (2C), 129.3 (2C), 129.7 (2C), 129.8, 129.9, 132.6, 133.1, 135.4, 137.3, 150.6, 150.9, 163.5, 164.3, 165.3, 165.8 ppm; MS (70 eV): m/z (%): 588 (M^+ , 0.8), 362 (13), 105 (100), 77 (23); HRMS calculated for $C_{36}H_{28}O_8$: 588.1784, found 588.1801.

General procedure for the reaction of 3a with secondary amines: 1.0 mmol of **3a** (588.6 mg) was dissolved in CH_2Cl_2 or dichloroethane depending on the temperature of the reaction. 1.0 - 2.0 mmol of the corresponding secondary amine was added and the reaction was stirred at room temperature or 60°C (see table 1) and it was followed by TLC analysis. The solvent was removed under reduced pressure. 1H NMR of the crude reaction products revealed the diastereoselectivity of the reaction by integration of the appropriate signals. This was followed by isolation of the desired products by flash column chromatography (silica gel, appropriate mixtures of n-hexane/ $EtOAc$).

(S,Z)-3-((S)-1-(diallylamino)-2-methoxy-2-oxoethyl)-4-(2-methoxy-2-oxoethylidene)-1,2-diphenylcyclobut-2-en-1-yl benzoate (15a): white solid; m.p. 143–144 °C. 1H NMR (400 MHz, $CDCl_3$): δ 3.43 (s, 3H), 3.44-3.50 (m, 2H), 3.63 (dd, 2H, $^3J(H,H) = 13.9$ and 5.3 Hz), 3.75 (s, 3H), 4.89 (s, 1H), 5.18-5.27 (m, 4H), 5.88 (s, 1H), 5.92-6.00 (m, 2H), 7.25-7.32 (m, 4H), 7.38 (t, 2H, $^3J(H,H) = 7.6$ Hz), 7.45 (t, 2H, $^3J(H,H) = 7.6$ Hz), 7.53-7.61 (m, 3H), 7.77 (d, 2H, $^3J(H,H) = 7.6$ Hz), 8.16 (d, 2H, $^3J(H,H) = 7.6$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.8, 52.0, 53.7 (2C), 61.1, 86.6, 102.4, 118.3 (2C), 125.6 (2C), 127.7, 128.28 (2C), 128.33 (2C), 128.7 (2C), 129.0 (2C), 129.8 (2C), 130.1, 130.2, 130.8, 132.8, 135.3 (2C), 139.0, 140.8, 159.0, 159.8, 164.1, 165.4, 170.0 ppm; MS (70 eV): m/z (%): 587 (M^+ , 0.2), 22 (1.9), 505 (13), 504 (42), 382 (6.2), 346 (9.0), 105 (100); elemental analysis calcd (%) for $C_{35}H_{33}NO_6$: C 74.58; H 5.90; N 2.49; found: C 74.22; H 6.07; N 2.39.

(S,Z)-3-((S)-1-(benzyl(methyl)amino)-2-methoxy-2-oxoethyl)-4-(2-methoxy-2-oxoethylidene)-1,2-diphenylcyclobut-2-en-1-yl benzoate (15b): white solid; m.p. 140–142 °C. 1H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 3.44 (s, 3H), 3.80 (s, 3H), 3.98 (s, 2H), 4.65 (s, 1H), 5.94 (s, 1H), 7.25-7.40 (m, 9H), 7.43-7.47 (m, 4H), 7.53-7.59 (m, 3H), 7.75-7.77 (m, 2H), 8.13-8.15 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.2, 50.8,

51.1, 59.3, 64.1, 86.6, 102.6, 125.6 (2C), 127.3, 127.8, 128.30 (4C), 128.37 (2C), 128.8 (2C), 129.0 (2C), 129.5 (2C), 129.6, 129.8 (2C), 130.0, 130.3, 130.7, 132.9, 138.3, 139.0, 159.1, 159.7, 164.2, 165.4, 169.8 ppm; MS (70 eV): m/z (%): 587 (M^+ , 0.8), 529 (39), 528 (100), 105 (78), 91 (55), 77 (20); HRMS calculated for $C_{37}H_{33}NO_6$: 587.2308, found 587.2284.

(S,Z)-3-((S)-1-(dibenzylamino)-2-methoxy-2-oxoethyl)-4-(2-methoxy-2-oxoethylidene)-1,2-diphenylcyclobut-2-en-1-yl benzoate (15c): white solid; m.p. 175–176 °C. 1H NMR (400 MHz, $CDCl_3$): δ 3.43 (s, 3H), 3.82 (s, 3H), 4.04 (d, 2H, $^3J(H,H) = 13.0$ Hz), 4.27 (d, 2H, $^3J(H,H) = 13.0$ Hz), 4.79 (s, 1H), 5.77 (s, 1H), 7.11-7.15 (m, 2H), 7.22-7.44 (m, 18H), 7.51-7.55 (m, 1H), 7.76-7.79 (m, 2H), 8.09-8.11 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.8, 52.0, 54.7 (2C), 58.9, 86.4, 101.7, 125.5 (2C), 127.2 (2C), 127.7, 128.2 (4C), 128.27 (2C), 128.29 (2C), 128.6, 128.7 (2C), 129.1 (2C), 129.7 (2C), 129.8 (2C), 130.0 (4C), 130.2, 130.7, 132.8, 138.9, 140.5, 159.8, 160.9, 163.9, 165.3, 170.8 ppm; IR ($CHCl_3$): $\nu = 3063.8, 3007.5, 2952.8, 1736.8, 1600.6, 1494.2, 1450.9, 1436.0, 1353.8, 1278.2$ cm^{-1} ; MS (70 eV): m/z (%): 663 (M^+ , 2.6), 605 (45), 604 (100), 572 (14), 541 (26), 105 (81), 91 (95); elemental analysis calcd (%) for $C_{43}H_{37}NO_6$: C 77.81; H 5.62; N 2.11; found: C 77.87; H 5.93; N 1.96.

(S,Z)-3-((S)-1-(bis(4-methoxybenzyl)amino)-2-methoxy-2-oxoethyl)-4-(2-methoxy-2-oxoethylidene)-1,2-diphenylcyclobut-2-en-1-yl benzoate (15d): pale yellow solid; m.p. 170–171 °C. 1H NMR (400 MHz, $CDCl_3$): δ 3.42 (s, 3H), 3.80 (s, 6H), 3.81 (s, 3H), 3.96 (d, 2H, $^3J(H,H) = 13.1$ Hz), 4.20 (d, 2H, $^3J(H,H) = 13.1$ Hz), 4.78 (s, 1H), 5.75 (s, 1H), 6.85-6.88 (m, 4H), 7.11-7.16 (m, 2H), 7.22-7.39 (m, 10H), 7.41-7.44 (m, 2H), 7.51-7.55 (m, 1H), 7.77-7.79 (m, 2H), 8.09-8.11 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.8, 52.0, 53.9 (2C), 55.2 (2C), 58.7, 86.4, 101.7, 113.6 (4C), 125.5 (2C), 127.7, 128.26 (2C), 128.30 (2C), 128.6 (2C), 129.1 (2C), 129.7, 129.8 (2C), 130.3, 130.7, 131.1 (4C), 132.8 (2C), 138.9, 140.5, 158.8 (2C), 160.9, 163.9, 165.3, 170.7 ppm, and two carbon signals buried under the aromatic region; MS (70 eV): m/z (%): 723 (M^+ , 0.6), 664 (15), 122 (13), 121 (100), 105 (18), 77 (8.6); HRMS calculated for $C_{45}H_{41}NO_6$: 723.2832, found 723.2813.

(S,Z)-3-((S)-2-methoxy-2-oxo-1-(pyrrolidin-1-yl)ethyl)-4-(2-methoxy-2-oxoethylidene)-1,2-diphenylcyclobut-2-en-1-yl benzoate (15e): Major isomer; pale yellow oil. 1H NMR (400 MHz, $CDCl_3$): δ 1.81-1.88 (m, 4H), 2.71-2.86 (m, 4H), 3.43 (s, 3H), 3.80 (s, 3H), 4.45 (s, 1H), 6.02 (s, 1H), 7.24-7.54 (m, 11H), 7.67-7.75 (m, 2H), 8.12-8.17 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 50.8, 52.4 (2C), 52.6 (2C), 65.8, 86.7, 103.0, 125.6 (2C), 127.7, 128.2 (2C), 128.4 (2C), 128.6, 128.8 (2C), 129.8 (2C), 129.8 (2C), 130.2, 130.8, 132.9, 139.0, 141.3, 157.1, 159.1, 164.2, 165.6, 169.4 ppm; IR ($CHCl_3$): $\nu = 3013.2, 2976.4, 1725.9, 1586.9, 1493.4, 1448.4, 1436.6, 1346.9, 1278.0, 1229.2, 1171.7, 1126.9$ cm^{-1} ; MS (70 eV): m/z (%): 537 (M^+ , 8.4), 479 (18), 478 (100), 415 (15), 226 (12), 105 (92), 77 (21); HRMS calculated for $C_{33}H_{31}NO_6$: 537.2151, found 537.2147. Characteristic signals for the minor isomer: 1H NMR (400 MHz, $CDCl_3$): δ 3.45 (s, 3H), 3.80 (s, 3H), 4.23 (s, 1H), 5.89 (s, 1H).

(S,Z)-3-((S)-2-methoxy-1-morpholino-2-oxoethyl)-4-(2-methoxy-2-oxoethylidene)-1,2-diphenylcyclobut-2-en-1-yl benzoate (15f): pale yellow solid; m.p. 163–164 °C. 1H NMR (400 MHz, $CDCl_3$): δ 2.70-2.77 (m, 2H), 2.87-2.94 (m, 2H), 3.44 (s, 3H), 3.79 (s, 3H), 3.81-3.85 (m, 4H), 4.49 (s, 1H), 6.12 (s, 1H), 7.27-7.31 (m, 4H), 7.34-7.38 (m, 2H), 7.45-7.49 (m, 2H), 7.55-7.58 (m, 1H), 7.62-7.64 (m, 2H), 7.68-7.71 (m, 2H), 8.15-8.17 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.8, 51.6 (2C), 52.3, 67.0 (2C), 67.1, 86.5, 103.4, 125.5 (2C), 127.8, 128.3 (2C), 128.36, 128.40 (2C), 128.7 (2C), 128.9 (2C), 129.8 (2C), 130.4, 130.6, 133.0, 138.8, 139.9, 158.7, 158.8, 164.3, 165.4, 168.7 ppm; IR ($CHCl_3$): $\nu = 3011.5, 1724.9, 1600.5, 1436.1, 1278.4, 1214.1, 1116.3, 1026.0$ cm^{-1} ; MS (70 eV): m/z (%): 553 (M^+ , 1.0), 494 (54), 431 (28), 286 (2.8), 215 (4.7), 105 (100), 77 (31); elemental analysis calcd (%) for $C_{33}H_{31}NO_7$: C 71.60; H 5.64; N 2.63; found: C 71.49; H 5.87; N 2.44.

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Keywords: *anti*-Michael / cyclobutene / amino acid / steric strain / allylic rearrangement

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FULL PAPER

Key Topic: anti-Michael addition

David Tejedor,*Gabriela Méndez-Abt,
Javier González-Platas, Israel
Fernández and Fernando García-
Tellado*

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H-bond Controlled **anti-aza-Michael**
Addition: Diastereoselective
Synthesis of Cyclobutene-containing
Amino Acid Derivatives.

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H-Bond makes the difference. The stereochemical outcome of the nucleophilic addition of secondary amines on the fully-substituted cyclobutanic platform shown in the Figure is governed by a $\text{NH}\cdots\text{O}=\text{C}$ interaction between the incoming amine and the benzoate leaving group. This interaction biases the amine addition by the same face of the leaving group to afford the most kinetically accessible amino acid