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Diels–Alder Reactions of α-Amido Acrylates with *N*-Cbz-1,2-dihydropyridine and Cyclopentadiene

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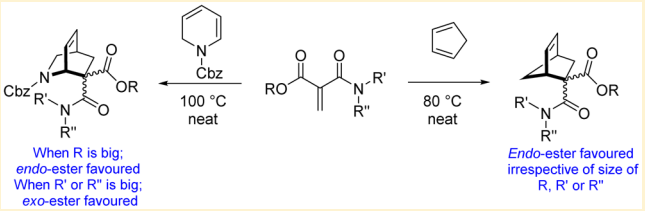
Supporting Information

ABSTRACT: Thermal Diels–Alder reactions of α-amido acrylates with *N*-Cbz-1,2-dihydropyridine and cyclopentadiene have been explored to investigate the factors influencing the *endo*/*exo* selectivity. For the dihydropyridine, steric factors allowed the diastereoselectivity to be modulated to favor either *endo*- or *exo*-ester adducts. For cyclopentadiene, the *endo*-ester adducts were favored regardless of steric perturbation, although catalysis by bulky Lewis acids increased the proportion of *exo*-ester adducts in some cases. These Lewis acids were incompatible with the dihydropyridine diene as they induced its decomposition.



Since its discovery in 1928, the Diels–Alder (DA) reaction has fundamentally changed the landscape of organic synthesis.[1] It allows for the rapid generation of molecular complexity and has served as a pivotal transformation in many complex natural product syntheses.[2] Our focus here is on DA reactions of *N*-carbalkoxy-1,2-dihydropyridines, which are frequently employed for the synthesis of isoquinuclidines.[3] This azabicyclo[2.2.2]octane unit is a common structural motif in many natural product classes, notably Iboga[4] and related Catharanthus[5] alkaloids (Figure 1).

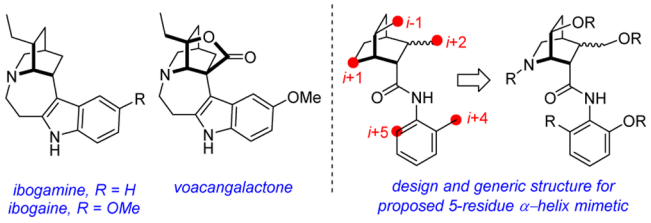


Figure 1. Examples of Iboga and Catharanthus alkaloids having the isoquinuclidine core, and our target isoquinuclidine-based α-helix mimetic.

In our efforts toward the synthesis of 5-residue, multiface α-helix mimetics based on an isoquinuclidine core (Figure 1),[6] we envisaged that an attractive, convergent strategy by which to access this skeleton would be via reaction of dienophile **1** with *N*-Cbz-1,2-dihydropyridine (Figure 2).

NMR studies and a single crystal X-ray structure determination (see Supporting Information (SI)) on the major product revealed that this DA reaction afforded exclusively the undesired *exo*-ester isomer **2**. Looking to understand this selectivity, we were surprised to find only limited literature precedent for the use of α-amido acrylates, or

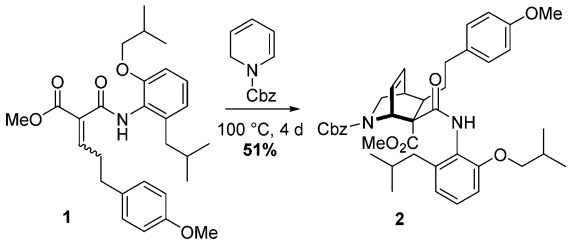


Figure 2. DA reaction between trisubstituted alkene **1** and *N*-Cbz-1,2-dihydropyridine.

β-substituted derivatives thereof, in DA reactions. Published reports are limited to cyclic compounds in which the nitrogen is constrained as a lactam,[7,8] part of a quinolone,[9] or part of an oxazine-2,4-dione.[10] Consequently, we decided to probe the reactivity of acyclic α-amido acrylates as dienophiles in DA reactions to determine the factors influencing their *endo*/*exo* selectivity. In particular, we wanted to investigate the influence of steric and electronic factors in controlling this diastereoselection. To this end, we prepared an array of β-unsubstituted-α-amido acrylates as test dienophiles. These substrates were chosen for three reasons: first, to preclude alkene isomerization;[11] second, because only two diastereoisomeric products can form; and third, because they show increased reactivity compared to β-substituted congeners. The α-amido acrylates were reacted with both *N*-Cbz-1,2-dihydropyridine and cyclopentadiene to allow an assessment of the role of the nitrogen substituent in the former dienophiles.[12]

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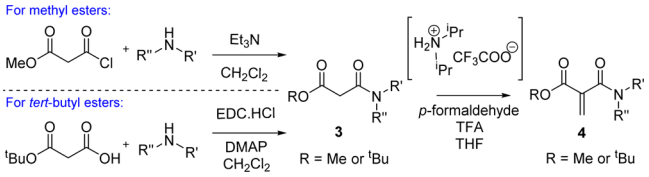
The α-amido acrylates were synthesized in two steps starting from commercially available methyl malonyl chloride or mono-*tert*-butyl malonate via amide bond formation followed by Mannich condensation−elimination (Scheme 1).[13]

Scheme 1. Method of Synthesis of α-Amido Acrylates 4



Rapid polymerization was observed upon attempted isolation of some α-amido methyl acrylates containing a secondary amide (*e.g.*, where R′ = Me or Ph and R″ = H), whereas no polymerization was apparent with tertiary amides. Presumably the secondary amides are both sufficiently nucleophilic and sterically unencumbered to allow for anionic polymerization via a 1,4-addition pathway. By contrast, introducing 2,2-dimethyl substitution, or bulky groups on the aryl ring of the secondary amide, inhibits polymerization allowing the dienophiles to be stored at room temperature for weeks without noticeable decomposition.

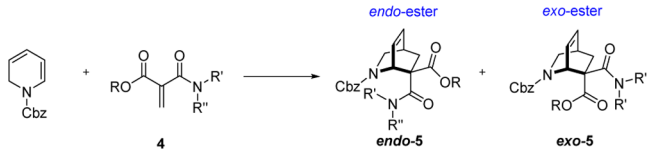
1,2-Dihydropyridines typically require heating to achieve efficient DA reactions, particularly given that they are unstable in the presence of many Lewis acids,[14] and so thermal DA reactions with *N*-Cbz-1,2-dihydropyridine were investigated first (Table 1).

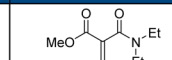
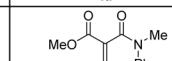
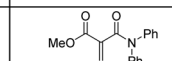
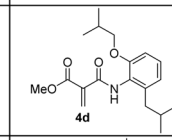
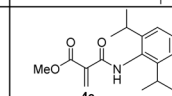
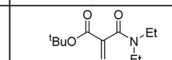
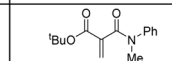
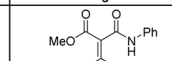
Overall, the *dr* of DA reactions of 1,2-dihydropryidines with α-amido acrylates appear to be dominated by the relative size of the substituents on the ester and amide. When the size of the groups on the ester and amide are both moderate, such as in dienophiles **4a** and **4b**, there is a slight preference for formation of the *endo*-ester isomer (entries 1 and 2). This intrinsic selectivity may reflect greater secondary orbital interactions between the ester and the diene due to the lower LUMO energy of an ester as compared to an amide. However, if the amide contains a large substituent, such as the 2,6-diisopropyl-phenyl group, the formation of the *exo*-ester is significantly more favored (entries 4 and 5). Presumably, the bulky aryl amide group sterically clashes with the *N*-Cbz group in the *endo*-ester transition state (TS) thus favoring the *exo*-ester-TS (Figure 3).

Diphenyl-substituted amide **4c** (entry 3) showed similar levels of *endo*-ester selectivity as amides **4a** and **4b**, indicating that the two aryl rings do not impose significant steric hindrance. The reactivity of the dienophiles increases significantly when an alkyl group is replaced by an aryl group in the amide, presumably as the result of lowering of the LUMO energy (cf. reaction times for *e.g.* entries 1 vs 2 vs 3). Replacing the methyl ester with a *tert*-butyl ester tipped the *dr* in favor of the *endo*-ester isomer (e.g., **4f** → **4g**, entries 6 and 7) and led to the highest *endo*-ester selectivities. This is consistent with the findings of Krow et al., who noted a greater preference for *endo* isoquinuclidine DA adducts when bulkier groups were present in simple acrylate esters.[3a] The *gem*-dimethyl substituted dienophile **4h** was found to be unreactive under the thermal DA conditions (entry 8).

To exclude the possibility that *retro*-DA readdition could be occurring, which would invalidate a TS-based rationalization of the selectivity trends, a mixture of the DA-adducts ***endo*-5e** and

Table 1. Diels−Alder Reactions between *N*-Cbz-1-2-dihydropyridine and α-Amido Acrylates 4a−h



Entry	Dienophile	*dr*[b] *Endo : Exo*	Reaction Time	Combined Isolated Yield
1	 4a	58 : 42	7 d	50%
2	 4b	62 : 38	3 d	68%
3	 4c	69 : 31	6.5 h	86%
4	 4d	24 : 76	16 h	58%
5	 4e	20 : 80	2.5 h	66%[c]
6	 4f	78 : 22	7 d[d]	37%
7	 4g	94 : 6	6 d[d]	48%
8	 4h	*No reaction*	5 d	-

[a]Reaction conditions unless otherwise specified: dienophile (1 equiv), *N*-Cbz-1,2-dihydropyridine (1.5−2.5 equiv), neat, sealed tube, under Ar, 100 °C. [b]*Endo*/*exo* ratios were determined by VT 1D and 2D NMR analysis and NOE experiments (see SI). [c]Neat for 2 h at 100 °C, then added dry toluene (0.5 M) and heated at 100 °C for 30 min. [d]Unreacted dienophile remaining.

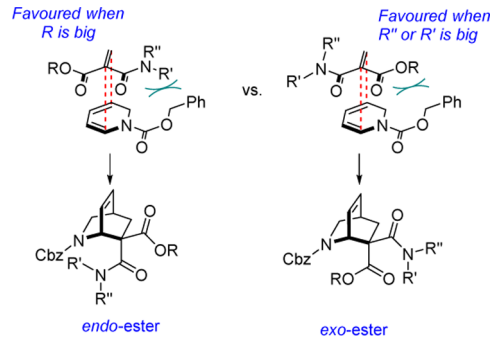


Figure 3. Proposed rationale for selectivity.

***exo*-5e** was heated in the presence of the diene at 100 °C for 5 days. No equilibration was observed, indicating that the initially observed *exo*/*endo* ratios reflect kinetic control. This is in agreement with previous studies.[15]

From a synthetic perspective, the ability to predictably promote either *exo* or *endo* product formation by appropriate choice of ester and amide substituents is attractive. Although the *exo*-ester configuration favored for the di-*ortho*-substituted diaryl amides **4d** and **4e** (*cf.* **1**, Figure 2) is not useful for our α-

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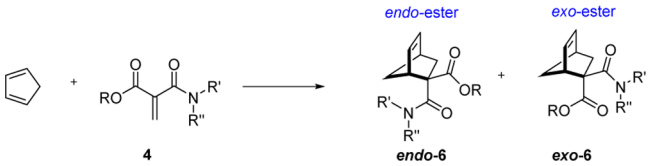
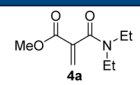
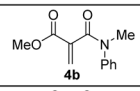
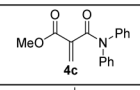
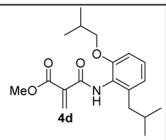
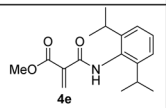
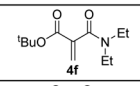
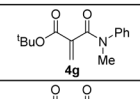
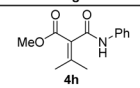
helix mimetic targets, the *endo*-ester configuration strongly favored for the *tert*-butyl esters **4f** and **4g** is potentially valuable for entry to the Iboga alkaloids (Figure 1).[4]

For comparison, we next investigated the corresponding DA reactions of cyclopentadiene as the diene (Table 2).

Table 2. DA Reactions between Cyclopentadiene and α-Amido Acrylates



Entry	Dienophile	*dr*[b] Endo : Exo	Reaction Time	Yield
1	 4a	78 : 22	24 h	45%
2	 4b	80 : 20	5 h	86%
3	 4c	70 : 30	80 mins	90%
4	 4d	84 : 16	16 h	58%
5	 4e	76 : 24	2.5 h	90%[c]
6	 4f	83 : 17	48 h	55%
7	 4g	81 : 19	24 h	67%
8	 4h	*No reaction*	5 d	-

[a]Reaction conditions unless otherwise specified: dienophile (1 equiv), cyclopentadiene (5 equiv), neat, sealed tube, under Ar, 80 °C. Reactions were stopped once all the dienophile was consumed. [b]*Endo*/*exo* ratios were determined by VT 1D and 2D NMR analysis and NOE experiments (see SI). [c]Neat for 2 h at 80 °C, then added dry toluene (0.5 M) and heated at 80 °C for a further 30 min.

By contrast to the DA reactions of 1,2-dihydropyridine, the diastereoselectivities obtained from reactions of cyclopentadiene do not appear to be influenced strongly by the steric demand of the amide and ester groups of the dienophile: all substrates afford the *endo*-ester with fairly high levels of selectivity (entries 1−7). As expected on account of strain relief, cyclopentadiene is more reactive than 1,2-dihydropyridine as evidenced by shorter reaction times, although the *gem*-dimethyl substituted dienophile **4h** was still unreactive (entry 8). The good levels of *endo*/*exo* selectivity and insensitivity toward steric congestion displayed in these reactions make them attractive for the synthesis of otherwise difficult to obtain *exo*-amide cyclopentadiene DA adducts.[1b,16]

The DA adducts ***endo*-6e** and ***exo*-6e** were heated in the presence of cyclopentadiene at 100 °C for 48 h; there was no observed epimerization after 24 h, although after 48 h traces could be detected (<5%). Given that all but one of the DA reactions (entry 6, 48 h) were complete within 24 h, the observed *endo*/*exo* ratios were concluded to be those of kinetic control.

Salvatella et al. have proposed that electrostatic rather than secondary orbital interactions are responsible for the high *endo* selectivity in the DA reaction between cyclopentadiene and acrolein.[17] They hypothesized that given the greater electronegativity of carbon relative to hydrogen, the δ+ charge on the hydrogen atom of the cyclopentadiene methylene facing the dienophile experiences a Coulombic repulsion as it approaches the δ+ charge on the carbonyl carbon thereby destabilizing the *exo*-TS. In our reactions, the lesser δ+ charge on the amide carbonyl carbon as compared to on the ester carbonyl might therefore be expected to give rise to less repulsion and so favor the *endo*-ester TS, as observed (Figure 4).

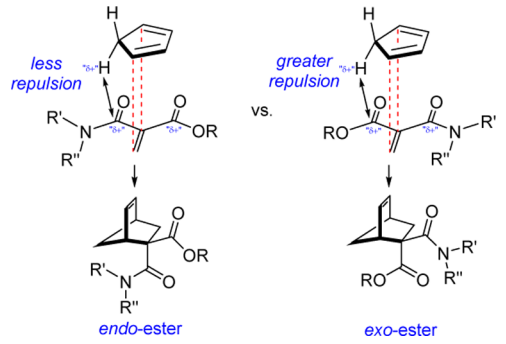


Figure 4. Proposed rationale for *endo*-ester selectivity.

Finally, we investigated whether Lewis acids could be used to perturb the *endo*/*exo* selectivity of the cyclopentadiene adducts. The effects of three Lewis acids were explored: Et_2AlCl, one of the most frequently utilized Lewis acid in DA reactions;[18] $B(C_6F_5)_3$, a bulky Lewis acid capable of overriding the typically observed *endo* selectivity in DA reactions of α,β-enals;[19] and TBSOTf, which has been reported to activate acrylamides but not acrylates in DA reactions with cyclopentadiene.[20] Although selective activation of the amide over the ester, or *vice versa*, in an α-amido acrylate was anticipated to be challenging, it was expected that this would be most feasible for sterically and/or electronically differentiated examples. Consequently, each of the three Lewis acids was reacted with the 2,6-diisopropylphenyl amide/methyl ester dienophile **4e** and the diethyl amide/*tert*-butyl ester dienophile **4f** (Table 3).

The reactions of the 2,6-diisopropylphenyl amide/methyl ester dienophile **4e** in the presence of 1 equiv of each of the three Lewis acids resulted in only minor deviations from the *endo*/*exo* ratio that was observed for the uncatalyzed reaction (entries 1−4). The Lewis acid catalyzed reactions were however significantly faster (2.5 h → 30 min), suggesting that these Lewis acids are likely either bridging between or at least equally activating the carbonyl groups of the 1,3-dicarbonyl moiety. It would therefore appear that, for dienophile **4e**, the bulky aryl amide and methyl ester carbonyls have balanced affinities for the Lewis acids (possibly the higher intrinsic bacisity of the amide is counterbalanced by steric factors). By contrast, the *dr*'s of reactions of the diethyl amide/*tert*-butyl ester dienophile **4f** were more strongly affected: Et_2AlCl slightly increased the *endo*-ester ratio (entry 6), whereas $B(C_6F_5)_3$ markedly increased the amount of the *exo*-

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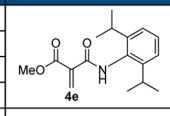
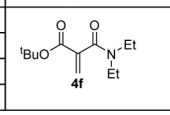
Table 3. DA Reactions between α-Amido Acrylates 4e and 4f and Cyclopentadiene in the Presence of Lewis Acids

Entry	Dienophile	Lewis Acid	*dr Endo : Exo*	Reaction Time	Yield
1[b]	 4e	-	76 : 24	2.5 h	90%
2		Et_2AlCl	77 : 23	30 mins	77%
3		$B(C_6F_5)_3$	76 : 24	30 mins	88%
4		TBSOTf	71 : 29	30 mins	75%
5[c]	 4f	-	83 : 17	48 h	55%
6		Et_2AlCl	88 : 12	2 h	66%
7		$B(C_6F_5)_3$	52 : 48	30 mins	67%
8		TBSOTf	50 : 50	2.5 h	52%

[a]Reaction conditions unless otherwise specified: dienophile (1 equiv), cyclopentadiene (10 equiv), Lewis acid (1 equiv), under Ar, rt, CH_2Cl_2 (0.1 M). [b]Same reaction as Table 2, entry 5. [c]Same reaction as Table 2, entry 6.

ester formed (entry 7), and TBSOTf similarly increased the amount of the *exo*-ester (entry 8). It would appear therefore that for dienophile **4f** the alkyl amide carbonyl displays stronger affinity than the *tert*-butyl ester carbonyl for the two most bulky Lewis acids (presumably because the bulky *tert*-butyl group limits coordination to the ester carbonyl). Finally, TMSOTf was briefly explored as a nonbulky trialkyl silyl triflate, but it was found to be incompatible with our reaction conditions.

In conclusion, we have explored the use of α-amido acrylates as dienophiles in DA reactions with *N*-Cbz-1,2-dihydropyridine and cyclopentadiene. We found that the *endo*/*exo* selectivity in the DA reactions with the dihydropyridine is strongly influenced by steric factors, allowing access to good levels of selectivity favoring either isomer. By contrast, when cyclopentadiene is used as the diene, the *endo*/*exo* selectivity is relatively unaffected by steric factors and electronic factors favor the *endo*-ester product. Lewis acid catalysis of the reactions is not possible for the dihydropyridine cases due to decomposition of these dienes, but for the cyclopentadiene cases, significant rate accelerations are achieved and increased proportions of *exo*-ester products can be formed by using bulky Lewis acids [*e.g.*, $B(C_6F_5)_3$ and TBSOTf] in conjunction with α-amido acrylates designed to allow coordination preferentially to the amide carbonyl rather than the ester carbonyl (*e.g.*, acrylate **4f**). As the result of the trends revealed in this work, we anticipate that α-amido acrylates could find wide utility in the stereocontrolled synthesis of isoquinuclidine-containing natural and unnatural products.

EXPERIMENTAL SECTION

***N*-Cbz-1,2-dihydropyridine.**[21] Pyridine (6 mL, 74.2 mmol) in MeOH (90 mL) was treated with $NaBH_4$ (2.81 g, 74.2 mmol). The reaction mixture was cooled to −78 °C before carefully adding benzylchloroformate (10.4 mL, 74.2 mmol) over a 1 h period via a dropping funnel. The reaction mixture was stirred at −78 °C for 2 h, poured into ice−water (a gas presumed to be H_2 was evolved), and extracted with CH_3Cl (4 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude material as an off-white oil. FC (flash chromatography) purification (*n*-hexane/Et_2O 20:1 → 5:1) afforded the 1,2-dihydropyridine as a pale yellow oil (5.49 g, 34%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50−7.30 (m, 5H), 6.87−6.62 (m, 1H), 5.90−5.77 (m, 1H), 5.58−5.41 (m, 1H), 5.28−5.09 (m, 3H), 4.40 (br s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz,): δ 149.8, 136.0, 128.6, 128.3, 128.1, 125.6, 121.9, 119.2, 105.0, 67.8, 43.6. IR (neat): ν = 3385, 3036, 2924, 2854, 1696, 1497, 1453, 1417, 1310, 1219, 1154, 1118, 1047, 1024, 735, 696. HRMS (Cl^+): *m*/*z* calcd for $C_{13}H_{14}NO_2$ 216.1025 $[M + H]^+$, found 216.1019.

Methyl 2-((2-Isobutoxy-6-isobutylphenyl)carbamoyl)-5-(4-methoxyphenyl)pent-2-enoate (1). A solution of α-amidoester **3d** (180 mg, 0.56 mmol) in CH_2Cl_2 (1.5 mL) in a round-bottom flask was cooled to 0 °C in an ice bath. To the cooled solution was added $TiCl_4$ by syringe (1 M solution in CH_2Cl_2, 0.62 mL, 0.62 mmol) dropwise over 10 min. The resulting mixture was stirred with cooling for 30 min at 0 °C, then 3-(4-methoxyphenyl)propanal (101 mg, 0.62 mmol) was added (diluted in 1.5 mL CH_2Cl_2) by syringe. The reaction mixture was stirred for 10 min at 0 °C after which anhydrous pyridine (0.09 mL, 1.12 mmol) was then added dropwise (caution: exothermic). The reaction was allowed to warm gradually to rt and stirred for 4 h under N_2. The reaction mixture was poured over ice and extracted with EtOAc (×3). The organic solution was then washed with brine, dried over $MgSO_4$, and concentrated to dryness. The crude residue was purified by FC (*n*-hexane/EtOAc 7.1 → 8:3) to afford a mixture of *Z*:*E* isomers in a 29:71 ratio (199 mg, 76%). **Z-Isomer**: *Methyl (Z)-2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-5-(4-methoxyphenyl)pent-2-enoate:* ^1H NMR ($CDCl_3$, 400 MHz): δ 9.03 (s, 1H), 7.64 (t, *J* = 7.1 Hz, 1H), 7.18−7.09 (m, 3H), 6.88−6.82 (m, 2H), 6.80 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.74 (dd, *J* = 8.3, 1.2 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.71 (d, *J* = 6.3 Hz, 2H), 2.92−2.74 (m, 4H), 2.46 (d, *J* = 7.2 Hz, 2H), 2.11−1.97 (m, 1H), 1.92−1.78 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.0, 162.9, 161.9, 158.1, 154.6, 154.2, 154.1, 153.2, 140.1, 132.9, 129.5, 129.3, 128.7, 127.5, 127.3, 126.9, 122.2, 122.2, 114.0, 113.8, 109.6, 74.8, 74.6, 55.3, 55.2, 52.4, 52.2, 41.3, 41.2, 34.0, 33.9, 32.8, 31.9, 29.3, 29.2, 28.4, 28.3, 22.6, 19.3, 19.2. ***E*-Isomer**: *Methyl (E)-2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-5-(4-methoxyphenyl)pent-2-enoate:* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.19−7.08 (m, 3H), 6.87−6.69 (m, 4H), 3.82 (s, 3H), 3.75 (s, 3H), 3.70 (d, *J* = 6.6 Hz, 2H), 3.00 (q, *J* = 7.6 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.48 (d, *J* = 7.2 Hz, 2H), 2.06−1.92 (m, 1H), 1.91−1.77 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.9, 158.0, 154.2, 153.2, 140.3, 132.7, 129.5, 128.7, 127.5, 122.2, 114.0, 113.8, 109.6, 74.8, 55.2, 52.4, 41.2, 33.9, 31.9, 29.2, 28.3, 22.6, 19.3, 19.2. HRMS (ES) (of *E*:*Z* mixture): *m*/*z* calcd for $C_{28}H_{38}NO_5$ 468.2750 $[M + H]^+$, found 468.2744.

Methyl 3-(Diethylamino)-3-oxopropanoate (3a).[22] To a solution of methyl 3-chloro-3-oxopropanoate (0.7 mL, 6.53 mmol) in dry CH_2Cl_2 (32 mL) at 0 °C under N_2 was added diethylamine (1.35 mL, 13.05 mmol). The reaction was allowed to warm up to rt and stirred for 3 h. The reaction mixture was further diluted in CH_2Cl_2 and then sequentially washed with 1 M HCl solution, *sat.* $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to provide α-amido-ester **3a** as an orange oil (1.03 g, 91%). ^1H NMR ($CDCl_3$, 400 MHz): 3.75 (s, 3H), 3.44 (s, 2H), 3.40 (q, *J* = 7.4 Hz, 2H), 3.30 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.3, 165.1, 52.4, 42.7, 41.1, 40.3, 14.2, 12.8.

Methyl 3-(Methyl(phenyl)amino)-3-oxopropanoate (3b).[23] To a solution of methyl 3-chloro-3-oxopropanoate (0.5 mL, 4.52 mmol) in dry CH_2Cl_2 (23 mL) at 0 °C under N_2 was added *N*-methylaniline (0.44 mL, 4.11 mmol) after which a suspension resulted. Et_3N (0.69 mL, 4.93 mmol) was then added, and after initial white fumes, a clear yellow solution formed. The reaction was allowed to warm up to rt and stirred for 2 h under N_2. The reaction mixture was concentrated, diluted in EtOAc and then sequentially washed with 1 M HCl solution, *sat.* $NaHCO_3$ solution, and brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to provide α-amido-ester **3b** as an orange oil (840 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.46−7.31 (m, 3H), 7.25−7.19 (m, 2H), 3.67 (s, 3H), 3.30 (s, 3H), 3.22 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.2, 165.9, 143.5, 130.0, 128.3, 127.3, 52.3, 41.3, 37.5.

Methyl 3-(diphenylamino)-3-oxopropanoate (3c).[24] To a solution of methyl 3-chloro-3-oxopropanoate (0.90 mL, 8.40 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C under N_2 were added diphenylamine (1.18 g, 7.0 mmol) and then Et_3N (1.17 mL, 8.40 mmol). The reaction mixture was slowly allowed to warm up to rt and stirred for 2 h. The reaction mixture was further diluted in CH_2Cl_2 and then sequentially washed with 1 M HCl solution, *sat.* $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was recrystallized using *n*-hexane/Et_2O 1:2 to

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provide α-amido-ester **3c** as a pale yellow powder (820 mg, 43%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52−7.14 (m, 10H), 3.70 (s, 3H), 3.41 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.0, 166.0, 142.4, 130.0, 129.0, 128.7, 128.4, 126.5, 126.3, 52.4, 42.5. HRMS (ES): *m*/*z* calcd for $C_{16}H_{16}NO_3$ 270.1130 $[M + H]^+$, found 270.1143.

Methyl 3-((2-Isobutoxy-6-isobutylphenyl)amino)-3-oxopropanoate (3d). To a solution of methyl 3-chloro-3-oxopropionate (0.14 mL, 1.24 mmol) in dry CH_2Cl_2 (7 mL) was added Et_3N (0.20 mL, 1.42 mmol), and the solution was cooled to 0 °C. To this was added dropwise a solution of di-*ortho*-substituted aniline[25] (274 mg, 1.24 mmol) in dry CH_2Cl_2 (3 mL). The reaction mixture was stirred at 0 °C for 30 min. The solution was washed with a *sat.* NH_4Cl solution and extracted with CH_2Cl_2 (×2). The organics were combined, washed with brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by FC (*n*-hexane/EtOAc 4.1 → 7:3) to afford α-amido ester **3d** as a yellow oil (181 mg, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (*br* s, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.74 (dd, *J* = 8.2, 1.3 Hz, 1H), 3.81 (s, 3H), 3.71 (d, *J* = 6.3 Hz, 2H), 3.51 (s, 2H), 2.45 (d, *J* = 7.2 Hz, 2H), 2.14−2.00 (m, 1H), 1.91−1.77 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 6H), 0.88 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 127.7, 122.2, 109.6, 74.6, 52.5, 41.4, 41.2, 29.3, 28.4, 22.6, 19.2. IR (neat): ν = 3272, 2952, 2868, 1742, 1655, 1531, 1460, 1439, 1348, 1304, 1273, 1226, 1200, 1142, 1058, 727, 767. HRMS (ES): *m*/*z* calcd for $C_{18}H_{28}NO_4$ 322.2018 $[M + H]^+$, found 322.2000.

Methyl 3-((2,6-Diisopropylphenyl)amino)-3-oxopropanoate (3e). To a solution of methyl 3-chloro-3-oxopropanoate (0.68 mL, 6.40 mmol) in dry CH_2Cl_2 (26 mL) at 0 °C under N_2 were added 2,6-diisopropylaniline (1.0 mL, 5.3 mmol) and then Et_3N (0.89 mL, 6.4 mmol). The reaction mixture was slowly allowed to warm up to rt and stirred for 3 h. The reaction mixture was further diluted in CH_2Cl_2 and then sequentially washed with 1 M HCl solution, *sat.* $NaHCO_3$ solution, and brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by FC (*n*-hexane/Et_2O 4.1 → 7:3) to provide α-amido-ester **3e** as a fluffy white solid (1.27 g, 86%). Mp = 110−113 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (*br.* s, 1H), 7.34−7.28 (m, 1H), 7.23−7.16 (m, 2H), 3.83 (s, 3H), 3.56 (s, 2H), 3.04 (hept, *J* = 6.9 Hz, 2H), 1.20 [d, *J* = 6.9 Hz, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.6, 164.2, 145.9, 130.8, 128.5, 123.5, 52.7, 40.8, 28.9, 23.6. IR (neat): ν = 3235, 2966, 1751, 1648, 1529, 1437, 1337, 1277, 1255, 1155, 796, 745, 709. HRMS (ES): *m*/*z* calcd for $C_{16}H_{24}NO_3$ 278.1756 $[M + H]^+$, found 278.1762.

***tert*-Butyl 3-(Diethylamino)-3-oxopropanoate (3f).**[26] To a solution of DMAP (159 mg, 1.30 mmol) and diethylamine (0.67 mL, 6.49 mmol) in dry CH_2Cl_2 (26 mL) was added 3-(*tert*-butoxy)-3-oxopropanoic acid (1 mL, 6.49 mmol). The reaction mixture was stirred under N_2 for 2 h. The reaction mixture was then diluted further in CH_2Cl_2 and washed with 1 M HCL solution and brine (× 2) and dried over $MgSO_4$. The organic solution was then concentrated under reduced pressure to provide α-amido-ester **3f** as a colorless oil (1.21 g, 87%), with no purification necessary. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.39 (q, *J* = 7.1 Hz, 2H), 3.33 (s, 2H), 3.28 (q, *J* = 7.1 Hz, 2H), 1.47 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.1, 165.6, 81.8, 42.5, 40.1, 28.0, 14.2, 12.8.

***tert*-Butyl 3-(Methyl(phenyl)amino)-3-oxopropanoate (3g).**[23] To a solution of DMAP (159 mg, 1.30 mmol) and *N*-methylaniline (0.70 mL, 6.49 mmol) in dry CH_2Cl_2 (26 mL) was added 3-(*tert*-butoxy)-3-oxopropanoic acid (1 mL, 6.49 mmol). The reaction mixture was stirred under N_2 for 2 h. The reaction mixture was then diluted further in CH_2Cl_2 and washed with 1 M HCL solution and brine (×2) and dried over $MgSO_4$. The organic solution was concentrated under reduced pressure to provide α-amido-ester **3g** as a dark orange oil (1.50 g, 93%), with no purification necessary. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45−7.38 (m, 2H), 7.38−7.32 (m, 1H), 7.25−7.21 (m, 2H), 3.30 (s, 3H), 3.12 (s, 2H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.0, 166.5, 143.7, 129.9, 128.2, 127.3, 81.6, 42.7, 37.4, 28.0. IR (neat): ν = 2980, 2936, 1720, 1634, 1478, 1460, 1393, 1368, 131257, 1155, 1117, 850, 734, 701.

Methyl 3-Oxo-3-(phenylamino)propanoate (3h).[27] To a solution of methyl 3-chloro-3-oxopropanoate (0.5 mL, 4.52 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C under N_2 was added aniline (0.41 mL, 4.52 mmol) after which a suspension resulted. Et_3N (0.73 mL, 5.2 mmol) was then added, and after initial white fumes were observed, a clear yellow solution formed. The reaction was stirred at 0 °C for 2 h under N_2. The reaction mixture was concentrated under reduced pressure, diluted in EtOAc, and then sequentially washed with 1 M HCl solution, *sat.* $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by FC (*n*-hexane/EtOAc 4:1 → 3:2) to afford α-amido-ester **3h** as a yellow semisolid (865 mg, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.16 (*br* s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 3.81 (s, 3H), 3.49 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5, 162.7, 137.4, 129.0, 124.6, 120.1, 52.7, 41.3.

Methyl 2-(Diethylcarbamoyl)acrylate (4a). To a solution of methyl 3-(diethylamino)-3-oxopropanoate (**3a**, 400 mg, 2.31 mmol), *p*-formaldehyde (208 mg, 6.93 mmol) and $CF_3COONH_2{}^iPr_2$ salt (497 mg, 2.31 mmol) in dry THF (20 mL) was added TFA (18 μL, 0.23 mmol). The reaction mixture was then heated at 60 °C under N_2 for 18 h. The reaction mixture was diluted with EtOAc, washed with *sat.* NH_4Cl solution (×2) and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by FC (EtOAc/*n*-hexane 3:2 → 4:1) to give α-amido-acrylate **4a** as a pale yellow oil (248 mg, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.41 (d, *J* = 0.8 Hz, 1H), 5.83 (d, *J* = 0.8 Hz, 1H), 3.79 (s, 3H), 3.46 (q, *J* = 7.1 Hz, 2H), 3.23 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.3, 164.4, 138.4, 127.8, 52.5, 42.9, 39.0, 13.8, 12.6. IR (neat): ν = 1723, 1618, 1486, 1460, 1440, 1326, 1264, 1201, 1173, 1122. HRMS (ES): *m*/*z* calcd for $C_{12}H_{14}NO_3$ 220.0974 $[M + H]^+$, found 220.0968.

Methyl 2-(Methyl(phenyl)carbamoyl)acrylate (4b). To a solution of methyl 3-(methyl(phenyl)amino)-3-oxopropanoate (**3b**, 150 mg, 0.752 mmol), *p*-formaldehyde (65 mg, 2.17 mmol), and $CF_3COONH_2{}^iPr_2$ salt (156 mg, 0.72 mmol) in dry THF (7 mL) was added TFA (6 μL, 0.07 mmol). The reaction mixture was then heated at 60 °C under N_2 for 18 h. The reaction mixture was diluted with EtOAc, washed with *sat.* NH_4Cl solution (× 2) and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by FC (*n*-hexane/EtOAc 1:1) to give α-amido-acrylate **4b** as a pale yellow oil (115 mg, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.30−7.20 (m, 1H), 7.13 (d, *J* = 7.7 Hz, 2H), 6.21 (s, 1H), 5.85 (s, 1H), 3.60 (s, 3H), 3.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.4, 164.3, 143.3, 138.6, 130.3, 129.4, 127.6, 127.2, 52.1, 37.3. IR (neat): ν = 1725, 1648, 1595, 1496, 1435, 1377, 1264, 1201, 1160, 1112, 772, 699. HRMS (ES): *m*/*z* calcd for $C_{12}H_{14}NO_3$ 220.0974 $[M + H]^+$, found 220.0968.

Methyl 2-(Diphenylcarbamoyl)acrylate (4c). To a solution of methyl 3-(diphenylamino)-3-oxopropanoate (**3c**, 800 mg, 2.97 mmol), *p*-formaldehyde (268 mg, 8.91 mmol), and $CF_3COONH_2{}^iPr_2$ salt (640 mg, 2.97 mmol) in dry THF (20 mL) was added TFA (23 μL, 0.29 mmol). The reaction mixture was heated at 60 °C under N_2 for 20 h. The reaction mixture was then concentrated under reduced pressure, and the resulting residue purified by FC (Et_2O/*n*-hexane 7:3) to give α-amido-acrylate **4c** as a pale yellow oil (780 mg, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44−7.06 (m, 10H), 6.31 (s, 1H), 6.09 (s, 1H), 3.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.2, 164.2, 142.2, 139.3, 131.2, 129.2 (*br*), 128.8 (*br*), 127.5 (*br*), 126.5 (*br*), 52.2. IR (neat): ν = 1727, 1662, 1593, 1490, 1399, 1351, 1266, 1201, 1132, 974, 760. HRMS (ES): *m*/*z* calcd for $C_{17}H_{16}NO_3$ 282.1130 $[M + H]^+$, found 282.1142.

Methyl 2-((2-Isobutoxy-6-isobutylphenyl)carbamoyl)-acrylate (4d). To a solution of methyl 3-((2-isobutoxy-6-isobutylphenyl)amino)-3-oxopropanoate (**3d**, 65 mg, 0.20 mmol), *p*-formaldehyde (18 mg, 0.61 mmol), and $CF_3COONH_2{}^iPr_2$ salt (44 mg, 0.20 mmol) in dry THF (2 mL) was added TFA (2 μL, 0.02 mmol). The reaction mixture was heated at 60 °C under N_2 for 18 h. The reaction mixture was then concentrated under reduced pressure, and the resulting residue purified by FC (Et_2O/*n*-hexane 1:1) to give α-amido-acrylate **4d** a colorless oil (33 mg, 50%), which was used immediately in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.57 (s, 1H), 7.21 (d,

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J = 1.6 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 6.83 (d, J = 1.6 Hz, 1H), 6.80 (dd, J = 7.8, 1.3 Hz, 1H), 6.75 (dd, J = 8.2, 1.3 Hz, 1H), 3.89 (s, 3H), 3.71 (d, J = 6.3 Hz, 2H), 2.48 (d, J = 7.2 Hz, 2H), 2.04 (dh, J = 13.2, 6.5 Hz, 1H), 1.85 (dh, J = 13.6, 6.8 Hz, 1H), 0.97 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.9, 160.7, 154.1, 140.0, 138.7, 132.8, 127.4, 124.2, 122.1, 109.7, 74.6, 52.7, 41.3, 29.3, 28.4, 22.6, 19.2. IR (neat): ν = 3310, 2953, 2868, 1745, 1733, 1666, 1581, 1516, 1508, 1460, 1266, 1053, 776, 734. HRMS (ES): m/z calcd for $C_{19}H_{28}NO_4$ 334.2018 $[M + H]^+$, found 334.2028.

Methyl 2-((2,6-Diisopropylphenyl)carbamoyl)acrylate (4e). To a solution of methyl 3-((2,6-diisopropylphenyl)amino)-3-oxopropanoate (**3e**, 800 mg, 2.88 mmol), *p*-formaldehyde (260 mg, 8.65 mmol), and $CF_3COONH_2{}^iPr_2$ salt (620 mg, 2.88 mmol) in dry THF (20 mL) was added TFA (23 μL, 0.29 mmol). The reaction mixture was then heated at 60 °C under N_2 for 16 h. The reaction mixture was then concentrated under reduced pressure, and the resulting residue was purified by FC (*n*-hexane/Et_2O 7:3 → 3:7) to give α-amido-acrylate **4e** as an off-white fluffy solid (505 mg, 61%). Mp = 97−98 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.66 (s, 1H), 7.33−7.26 (m, 2H), 7.23−7.17 (m, 2H), 6.90 (d, J = 1.8 Hz, 1H), 3.92 (s, 3H), 3.05 (hept, J = 6.9 Hz, 2H), 1.20 [d, J = 6.9 Hz, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.2, 161.3, 145.8, 139.7, 132.3, 131.2, 128.2, 123.4, 52.8, 28.9, 23.6. IR (neat): ν = 3235, 2966, 1751, 1648, 1529, 1437, 1338, 1255, 1214, 1155, 745, 709. HRMS (ES): m/z calcd for $C_{17}H_{24}NO_3$ 290.1756 $[M + H]^+$, found 290.1758.

***tert*-Butyl 2-(Diethylcarbamoyl)acrylate (4f).** To a solution of the *tert*-butyl 3-(diethylamino)-3-oxopropanoate (**3f**, 1.2 g, 5.58 mmol), *p*-formaldehyde (503 mg, 16.7 mmol), and $CF_3COONH_2{}^iPr_2$ salt (1.2 g, 5.58 mmol) in dry THF (28 mL) was added TFA (43 μL, 0.56 mmol). The reaction mixture was heated at 60 °C under N_2 for 16 h. The reaction mixture was then concentrated under reduced pressure, and the resulting residue was purified by FC (*n*-hexane/Et_2O 3:2) to give α-amido-acrylate **4f** as a yellow oil (558 mg, 44%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.31 (d, 1H, J = 0.8 Hz), 5.76 (d, 1H, J = 0.8 Hz), 3.45 (q, J = 7.2 Hz, 2H), 3.21 (q, J = 7.1 Hz, 2H), 1.49 (s, 9H), 1.17 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.7, 162.9, 140.3, 126.7, 82.1, 42.6, 38.7, 28.0, 13.9, 12.4. IR (neat): ν = 2977, 2931, 1722, 1640, 1460, 1368, 1258, 1158, 1118, 851. HRMS (ES): m/z calcd for $C_{12}H_{22}NO_3$ 228.1600 $[M + H]^+$, found 228.1602.

***tert*-Butyl 2-(Methyl(phenyl)carbamoyl)acrylate (4g).** To a solution of *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate (**3g**, 1.29 g, 5.98 mmol), *p*-formaldehyde (540 mg, 17.95 mmol), and $CF_3COONH_2{}^iPr_2$ salt (1.29 g, 5.58 mmol) in dry THF (30 mL) was added TFA (46 μL, 0.56 mmol). The reaction mixture was heated at 60 °C under N_2 for 40 h. The reaction mixture was then concentrated under reduced pressure, and the resulting residue was purified by FC (*n*-hexane/Et_2O 4:1 → 3:2) to give α-amido-acrylate **4g** as a yellow oil (873 mg, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36−7.13 (m, 5H), 6.14 (s, 1H), 5.83 (s, 1H), 3.39 (s, 3H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.6, 143.4, 140.7, 129.2, 129.2, 127.2, 127.2, 81.8, 37.2, 27.9, 27.8. IR (neat): ν = 2976, 1715, 1650, 1595, 1496, 1394, 1368, 1272, 1257, 1149, 1110, 849, 768, 699. HRMS (ES): m/z calcd for $C_{15}H_{20}NO_3$ 262.1443 $[M + H]^+$, found 262.1447.

Methyl 3-Methyl-2-(phenylcarbamoyl)but-2-enoate (4h). A solution of methyl 3-oxo-3-(phenylamino)propanoate (150 mg, 0.77 mmol) in CH_2Cl_2 (4 mL) in a round-bottom flask was cooled to 0 °C in an ice bath. To the cooled solution, was added $TiCl_4$ by syringe (1 M solution in CH_2Cl_2, 0.85 mL, 0.85 mmol) dropwise over 10 min. The resulting mixture was stirred with cooling for 30 min at 0 °C, after which acetone (0.063 mL, 0.85 mmol) was added. The reaction mixture was stirred for 10 min at 0 °C before dropwise addition of anhydrous pyridine (0.13 mL, 1.55 mmol) (***Caution:*** very exothermic). The reaction was allowed to warm gradually to rt overnight and then poured over ice and extracted with EtOAc (×3). The organic solution was then washed with brine, dried over $MgSO_4$, and concentrated to dryness. The crude residue was purified by FC (*n*-hexane/EtOAc 4:1 → 3:2) to give the tetrasubstituted alkene **4h** as a white solid (137 mg, 76%). Mp = 137−142 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (*br* s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 3.78 (s, 3H), 2.17 (s, 3H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.1, 164.6, 155.1, 137.8, 129.1, 127.0, 124.5, 119.9, 52.0, 24.1, 22.6. IR (neat): ν = 3240, 1715, 1652, 1547, 1444, 1331, 1258, 1217, 1062, 762. HRMS (ES): m/z calcd for $C_{13}H_{16}NO_3$ 234.1130 $[M + H]^+$, found 234.1127.

General Procedure for DA Reactions between α-Amido Acrylates and *N*-Cbz-1,2-dihydropyridine (GP1). *N*-Cbz-1,2-dihydropyridine (1.5−2.5 equiv) and α-amido acrylate (1 equiv) were transferred to a Biotage microwave vial containing a Teflon-coated magnetic stirrer bar which was subsequently thoroughly purged with Ar prior to sealing. The reaction was then heated at 100 °C until consumption of the dienophile was observed by TLC analysis. The reaction mixture was directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

2-Benzyl 6-Methyl (1*R,4*S**,6*S**)-6-((2-Isobutoxy-6-isobutylphenyl)carbamoyl)-5-(4-methoxyphenethyl)-2-azabicyclo-[2.2.2]oct-7-ene-2,6-dicarboxylate (2).** According to **GP1**, *N*-Cbz-1,2-dihydropyridine (133 mg, 0.62 mmol) and methyl 2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-5-(4-methoxyphenyl)pent-2-enoate (**1**, 145 mg, 0.31 mmol; as a 29:71 mixture of *Z*:*E* isomers) were heated for 4 d. FC purification (*n*-hexane/EtOAc 4:1 → 3:2) afforded *exo*-ester **2** exclusively (108 mg, 51%). Mp = 39−40 °C. ^{1}H NMR and ^{13}C NMR: complex even at 398 K due to atropisomerism; see SI. HRMS (ES): m/z calcd for $C_{41}H_{51}N_2O_7$ 683.3696, found 683.3671. IR (neat): ν = 3387, 2954, 2928, 2868, 1740, 1693, 1584, 1512, 1457, 1416, 1366, 1335, 1245, 1179, 1115, 1054, 748. A single crystal X-ray structure determination was performed on this compound to confirm its structure; see SI PDF and CIF files.

2-Benzyl 6-Methyl (1*R,4*R**,6*R**)-6-(Diethylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-5a) and 2-Benzyl 6-Methyl (1*R**,4*R**,6*S**)-6-(Diethylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-5a).** According to **GP1**, *N*-Cbz-1,2-dihydropyridine (350 mg, 1.63 mmol) and methyl 2-(diethylcarbamoyl)acrylate (**4a**, 100 mg, 0.54 mmol) were heated for 7 d. FC purification (*n*-hexane/EtOAc 4:1 → 2:3) afforded a mixture of diastereoisomers ***endo*-5a:*exo*-5a** in a 58:42 ratio (120 mg, 50%). Isolated ***endo*-5a**, colorless paste. ^{1}H NMR (DMSO-d_6, 400 MHz, 378 K): δ 7.45−7.25 (m, 5H), 6.48−6.36 (m, 2H), 5.22−5.18 (m, 1H), 5.11−4.97 (*AB*, m, 2H), 3.64 (s, 3H), 3.40−3.09 (m, 5H), 2.91−2.82 (m, 2H), 1.76 (*br* s, 1H), 1.06−0.92 (m, 6H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 171.3, 166.0, 154.0, 136.7, 134.1, 130.6, 127.7, 127.0, 126.8, 65.4, 58.5, 51.6, 49.0, 45.3, 32.6, 29.8, 11.81. IR (neat): ν = 2978, 2957, 1731, 1699, 1638, 1417, 1293, 1245, 1211, 1114, 736, 699. HRMS (ES): m/z calcd for $C_{22}H_{29}N_2O_5$ 401.2076 $[M + H]^+$, found 401.2082. ***Exo*-5a** not fully separated from ***endo*-5a**, pale yellow paste. Distinguishable peaks only: ^{1}H NMR (DMSO-d_6, 400 MHz, 378 K): δ 6.51−6.45 (m, 1H), 6.33−6.25 (m, 1H), 5.14 (dd, J = 6.0, 0.8 Hz, 1H), 3.52 (s, 3H), 1.45 (dt, J = 12.8, 2.7 Hz, 1H), 1.32−1.19 (m, 1H). Distinguishable peaks only: ^{13}C NMR (DMSO-d_6, 101 MHz, 378 K): δ 171.5, 168.1, 153.7, 136.6, 132.9, 131.5, 127.7, 127.1, 65.6, 59.9, 51.8, 51.0, 30.3, 29.6, 21.3, 13.1.

2-Benzyl 6-Methyl (1*R,4*R**,6*R**)-6-(Methyl(phenyl)-carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-5b) and 2-Benzyl 6-Methyl (1*R**,4*R**,6*S**)-6-(Methyl-(phenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-5b).** According to **GP1**, *N*-Cbz-1,2-dihydropyridine (135 mg, 0.63 mmol) and methyl 2-(methyl(phenyl)carbamoyl)-acrylate (**4b**, 55 mg, 0.25 mmol) were heated for 3 d. FC purification (Et_2O/*n*-hexane 1:1 → 4:1) afforded a mixture of diastereoisomers ***endo*-5b:*exo*-5b** in a 62:38 ratio (74 mg, 68%). Isolated ***endo*-5b**, white solid. Mp = 83−85 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 398 K): δ 7.43−7.22 (m, 10H), 6.39−6.24 (m, 2H), 5.23 (dd, J = 5.8, 1.5 Hz, 1H), 5.19−5.06 (*AB*, m, 2H), 3.42 (s, 3H), 3.33 (d, J = 9.7 Hz, 1H), 3.11 (s, 3H), 2.88 (dt, J = 9.9, 2.7 Hz, 1H), 2.84−2.74 (m, 2H), 1.49 (dt, J = 13.2, 2.9 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 170.2, 167.1, 154.1, 142.6, 136.5, 133.4, 130.5, 128.4, 127.7, 127.6, 127.0, 126.9, 126.8, 65.5, 59.1, 51.1, 49.2, 45.2, 33.1, 29.6. IR (neat): ν = 1737, 1680, 1652, 1638, 1496, 1441, 1417, 1405, 1247, 1215, 1130, 1122, 990, 732. HRMS (ES): m/z calcd for $C_{25}H_{27}N_2O_5$ 435.1920 $[M + H]^+$, found 435.1928. Isolated ***exo*-5b**, off-white semisolid. ^{1}H NMR (DMSO-d_6, 400 MHz, 378 K): δ 7.43−7.25 (m, 8H), 7.16−7.10 (m,

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2H), 6.51 (ddd, J = 7.7, 5.9, 1.5 Hz, 1H), 6.33 (ddd, J = 7.8, 6.5, 1.2 Hz, 1H), 5.15 (dd, J = 6.0, 1.2 Hz, 1H), 5.08−4.96 (*AB*, m, 2H), 3.47 (s, 3H), 3.18−3.08 (m, 1H), 3.07 (s, 3H), 2.86−2.75 (m, 2H), 2.16 (d, J = 13.1 Hz, 1H), 1.62 (dt, J = 13.0, 2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz, 378 K): δ 170.5, 168.7, 153.6, 141.7, 136.5, 132.5, 131.9, 128.5, 127.7, 127.1, 127.1, 126.8, 124.3, 65.5, 60.2, 51.5, 51.0, 44.7, 37.8, 32.9, 29.6. IR (neat): ν = 1739, 1696, 1650, 1593, 1496, 1411, 1363, 1335, 1294, 1276, 1114. HRMS (ES): m/z calcd for $C_{25}H_{27}N_2O_5$ 435.1920 $[M + H]^+$, found 435.1924.

2-Benzyl 6-Methyl (1*R,4*R**,6*R**)-6-(Diphenylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-5c) and 2-Benzyl 6-Methyl (1*R**,4*R**,6*S**)-6-(Diphenylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-5c).** According to **GP1**, *N*-Cbz-1,2-dihydropyridine (467 mg, 2.17 mmol) and methyl 2-(diphenylcarbamoyl)acrylate (**4c**, 305 mg, 1.09 mmol) were heated for 6.5 h. FC purification (*n*-hexane/Et_2O 3:2 → 3:7) afforded a mixture of diastereoisomers ***endo*-5c**:***exo*-5c** in a 69:31 ratio (465 mg, 86%). Isolated ***endo*-5c**, white solid. Mp = 140−141 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, 398 K): δ 7.45−7.20 (m, 15H), 6.37−6.30 (m, 1H), 6.30−6.24 (m, 1H), 5.33 (d, J = 5.3 Hz, 1H), 5.23−5.10 (*AB*, *app* q, 2H, J = 15.5 Hz), 3.41 (s, 3H), 3.39−3.33 (m, 1H), 2.93 (dt, J = 9.9, 2.6 Hz, 1H), 2.88−2.78 (m, 2H), 1.50−1.43 (dt, 1H, J = 16.5, 3.5 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz, 398 K) δ 169.7, 167.8, 154.4, 142.3, 136.4, 133.3, 130.6, 128.3, 128.0, 127.6, 127.0, 126.8, 126.6, 65.7, 59.8, 51.1, 49.6, 45.2, 33.4, 29.6. IR (neat): ν = 2948, 1719, 1693, 1654, 1491, 1417, 1333, 1275, 1258, 1104, 768, 752, 706. HRMS (ES): m/z calcd for $C_{30}H_{29}N_2O_5$ 497.2076 $[M + H]^+$, found 497.2073. Isolated ***exo*-5c**, white solid. Mp = 72−75 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 398 K): δ 7.43−7.18 (m, 15H), 6.52 (ddd, J = 7.7, 5.9, 1.5 Hz, 1H), 6.39 (ddd, J = 7.9, 6.5, 1.2 Hz, 1H), 5.21 (dd, J = 5.9, 1.2 Hz, 1H), 5.03 (*AB*, *app*. q, J = 12.7 Hz, 2H), 3.51 (s, 3H), 3.10 (d, J = 10.0 Hz, 1H), 2.84−2.76 (m, 2H), 2.00 (dd, J = 13.2, 2.9 Hz, 1H), 1.82 (dt, J = 13.2, 2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 171.2, 170.0, 154.6, 142.6, 137.6, 133.3, 129.4, 129.3, 129.1, 128.7, 128.1, 128.0, 127.8, 66.6, 62.0, 52.5, 52.4, 34.1, 30.8. IR (neat): ν = 2952, 1740, 1695, 1661, 1491, 1410, 1333, 1292, 1274, 1212, 1107, 753, 693. HRMS (ES): m/z calcd for $C_{30}H_{29}N_2O_5$ 497.2076 $[M + H]^+$, found 497.2069.

2-Benzyl 6-Methyl (1*R,4*R**,6*R**)-6-((2-Isobutoxy-6-isobutylphenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-5d) and 2-Benzyl 6-Methyl (1*R**,4*R**,6*S**)-6-((2-Isobutoxy-6-isobutylphenyl)carbamoyl)-2-azabicyclo[2.2.2]-oct-7-ene-2,6-dicarboxylate (*exo*-5d).** According to **GP1**, *N*-Cbz-1,2-dihydropyridine (50 mg, 0.23 mmol) and methyl 2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)acrylate (**4d**, 30 mg, 0.09 mmol) were heated for 16 h. FC purification (*n*-hexane/Et_2O 7:3 → 1:1) afforded an inseparable mixture of diastereoisomers ***endo*-5d**:***exo*-5d** in a 24:76 ratio[28] (29 mg, 58%;): colorless oil. ***Endo*-5d**:***exo*-5d** mixture: ^{1}H NMR (DMSO-d_6, 400 MHz, 398 K): δ 8.18 (*br* s, 0.76H), 8.03 (*br* s, 0.24H), 7.41−7.23 (m, 5H), 7.19−7.05 (m, 1H), 6.86−6.72 (m, 2H), 6.54−6.37 (m, 2H), 5.47−5.36 (m, 1H), 5.18−5.04 (m, 2H), 3.72−3.59 (m, 5H), 3.35−3.22 (m, 1H), 3.02−2.90 (m, 2H), 2.82−2.69 (m, 1H), 2.45−1.95 (m, 4H), 1.92−1.77 (m, 1H), 1.02−0.95 (m, 6H), 0.84 (m, 6H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 171.7, 170.6, 169.9, 166.9, 154.4, 153.8, 139.9, 136.5, 133.5, 131.0, 130.0, 127.5, 127.5, 126.9, 126.9, 126.6, 126.5, 126.4, 126.4, 124.4, 120.9, 109.7, 109.7, 74.3, 65.7, 65.5, 60.6, 51.7, 51.5, 49.7, 49.2, 46.9, 45.5, 31.0, 30.2, 29.9, 29.7, 29.6, 27.3, 27.2, 27.1, 27.0, 21.7, 21.6, 21.6, 18.3, 18.2. IR (neat): ν = 2955, 2932, 2876, 1736, 1699, 1585, 1499, 1459, 1414, 1248, 1112, 1055, 749, 698. HRMS (ES): m/z calcd for $C_{32}H_{41}N_2O_6$ 549.2965 $[M + H]^+$, found 549.2982.

Methyl (1*R,4*S**,6*S**)-6-((2-Isobutoxy-6-isobutylphenyl)-carbamoyl)-2-isobutyl-2-azabicyclo[2.2.2]octane-6-carboxylate (*exo*-5dx).** To a solution of a mixture of *N*-Cbz-alkenes ***endo*-5d**:***exo*-5d** in a 24:76 ratio (23.8 mg, 0.043 mmol,) in MeOH (1 mL) were added NH_3 (7N *soln.* in MeOH, 31 μL, 0.22 mmol), isobutyraldehyde (12 μL, 0.13 mmol), and Pd/C (10% *wt.*, 9 mg, 0.0086 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 18 h. The reaction was concentrated to dryness, and the residue was then purified by FC (*n*-hexane/Et_2O 7:3) to afford the *N*-alkylated quinucidine ***exo5dx*** as a yellow oil (11.3 mg, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.22 (s, 1H), 7.08 (t, J = 7.9 Hz, 1H), 6.72 (dd, J = 15.6, 7.9 Hz, 2H), 3.73 (s, 3H), 3.71−3.62 (m, 2H), 3.29 (t, J = 2.5 Hz, 1H), 3.24−3.17 (m, 1H), 2.96−2.86 (m, 1H), 2.64 (dd, J = 11.5, 4.1 Hz, 1H), 2.49 (dd, J = 13.5, 7.0 Hz, 1H), 2.39 (dd, J = 13.4, 7.5 Hz, 1H), 2.32−2.24 (m, 1H), 2.18 (t, J = 11.0 Hz, 1H), 2.13−2.00 (m, 2H), 2.00−1.84 (m, 3H), 1.83−1.68 (m, 1H), 1.55 (d, J = 9.1 Hz, 2H), 1.40−1.30 (m, 1H), 1.03 (t, J = 6.6 Hz, 6H), 0.92−0.83 (m, 9H), 0.74 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.8, 172.6, 154.6, 141.0, 127.0, 123.8, 122.3, 109.4, 74.6, 64.5, 57.4, 55.5, 54.2, 52.4, 41.5, 31.8, 29.4, 28.5, 26.1, 25.8, 23.3, 22.8, 22.5, 21.3, 20.0, 19.5, 19.4, 18.1. HRMS (ES): m/z calcd for $C_{28}H_{45}N_2O_4$ 473.3379 $[M + H]^+$, found 473.3398.

2-Benzyl 6-Methyl (1*R,4*R**,6*R**)-6-((2,6-Diisopropylphenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-5e) and 2-Benzyl 6-Methyl (1*R**,4*R**,6*S**)-6-((2,6-Diisopropylphenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-5e).** According to **GP1**, *N*-Cbz-1,2-dihydropyridine (349 mg, 1.62 mmol) and methyl 2-((2,6-diisopropylphenyl)carbamoyl)acrylate (**4e**, 276 mg, 0.96 mmol) were heated for 2 h, after which dry toluene (0.2 mL) was added to aid solubility, and the mixture was heated at 100 °C for a further 30 min. FC purification (*n*-hexane/Et_2O 7:3 → 3:7) afforded a mixture of diastereoisomers ***endo*-5e**:***exo*-5e** in a 20:80 ratio (319 mg, 66%): Isolated ***endo*-5e**, colorless paste. ^{1}H NMR (DMSO-d_6, 400 MHz, 398 K): δ 8.64 (*br* s, 1H), 7.42−7.08 (m, 10H), 6.48 (dd, J = 4.4, 3.2 Hz, 2H), 5.50 (dd, J = 4.2, 2.9 Hz, 1H), 5.12−5.05 (m, 2H), 3.70 (s, 3H), 3.28 (dd, J = 10.1, 2.1 Hz, 1H), 3.07−2.92 (m, 4H), 2.55 (dd, J = 13.6, 2.5 Hz, 1H), 2.15 (dt, J = 13.6, 3.1 Hz, 1H), 1.10 (*app*. dd, J = 6.9, 5.3 Hz, 12H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 170.2, 166.8, 154.9, 145.9, 145.8, 136.2, 134.5, 131.6, 130.8, 127.6, 127.2, 126.9, 126.8, 126.6, 126.5, 125.8, 122.2, 122.1, 122.0, 65.7, 60.1, 51.5, 49.4, 46.4, 30.51, 29.7, 27.1, 22.7, 22.6. IR (neat): ν = 3371, 2961, 1731, 1695, 1682, 1506, 1496, 1456, 1417, 1334, 1249, 1203, 1120. HRMS (ES): m/z calcd for $C_{30}H_{37}N_2O_5$ 505.2702 $[M + H]^+$, found 505.2706. Isolated ***exo*-5e**, colorless paste. ^{1}H NMR (DMSO-d_6, 400 MHz, 398 K): δ 8.72 (*br* s, 1H), 7.43−7.29 (m, 5H), 7.26−7.19 (m, 1H), 7.15−7.07 (m, 2H), 6.58−6.39 (m, 2H), 5.47 (dd, J = 5.7, 1.5 Hz, 1H), 5.15−5.05 (*AB*, m, 2H), 3.62 (s, 3H), 3.34−3.26 (m, 1H), 3.06−2.97 (m, 2H), 2.97−2.90 (m, 2H), 2.69 (dd, J = 13.5, 2.5 Hz, 1H), 2.03 (dt, J = 13.5, 2.9 Hz, 1H), 1.11 (dd, J = 14.1, 6.9 Hz, 12H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 170.5, 167.7, 153.8, 145.9, 136.6, 133.7, 131.7, 130.9, 127.6, 126.9, 126.8, 126.6, 122.2, 122.0, 65.4, 60.7, 51.3, 49.4, 45.7, 31.1, 29.7, 26.9, 22.6, 22.5. IR (neat): ν = 3323, 2961, 1737, 1692, 1680, 1498, 1415, 1336, 1245, 1114. HRMS (ES): m/z calcd for $C_{30}H_{37}N_2O_5$ 505.2702 $[M + H]^+$, found 505.2727.

2-Benzyl 6-(*tert*-Butyl)(1*R,4*R**,6*R**)-6-(diethylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-5f) and 2-Benzyl 6-(*tert*-Butyl)(1*R**,4*R**,6*S**)-6-(diethylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-5f).** According to **GP1**, *N*-Cbz-1,2-dihydropyridine (568 mg, 2.64 mmol) and *tert*-butyl 2-(diethylcarbamoyl)acrylate (**4f**, 300 mg, 1.31 mmol) were heated for 7 days. FC purification (*n*-hexane/EtOAc 4:1 → 2:3) afforded a mixture of diastereoisomers ***endo*-5f**:***exo*-5f** in a 78:22 ratio (219 mg, 37%): Isolated ***endo*-5f**, colorless paste. ^{1}H NMR (DMSO-d_6, 400 MHz, 398 K): δ 7.42−7.24 (m, 5H), 6.44−6.34 (m, 2H), 5.26−5.12 (dd, J = 3.2, 3.6 Hz, 1H), 5.11−5.00 (*AB*, m, 2H), 3.42−3.14 (m, 5H), 2.89−2.82 (m, 2H), 2.49−2.44 (m, 1H), 1.82 (*br* d, J = 12.7 Hz, 1H), 1.40 (s, 9H), 1.06 (*app*. t, J = 7.0 Hz, 6H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 169.4, 166.6, 154.0, 136.7, 133.5, 130.6, 127.5, 126.8, 126.6, 81.0, 65.3, 59.3, 49.3, 45.5, 32.3, 29.9, 26.9, 11.7. IR (neat): ν = 2972, 2936, 1698, 1638, 1411, 1367, 1332, 1294, 1273, 1250, 1157, 1114, 761, 698. HRMS (ES): m/z calcd for $C_{25}H_{35}N_2O_5$ 443.2546 $[M + H]^+$, found 443.2551. ***Exo*-5f** not fully separated from ***endo*-5f**, pale yellow paste. Distinguishable peaks only: ^{1}H NMR (DMSO-d_6, 400 MHz, 398 K): δ 6.50 (ddd, J = 7.9, 5.9, 1.6 Hz, 1H), 6.30−6.24 (m, 1H), 3.15−3.04 (m, 2H), 2.95 (dt, J = 10.1, 2.7 Hz, 1H), 1.37 (s, 9H). Distinguishable peaks only: ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 134.0, 132.3, 130.8, 127.4, 126.8, 126.3, 65.4, 51.1, 45.1, 38.2, 32.2, 29.7, 27.6, 26.6, 25.0, 22.6, 12.5.

2-Benzyl 6-(*tert*-Butyl)(1*R,4*R**,6*R**)-6-(Methyl(phenyl)-carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate**

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(*endo*-5g) and 2-Benzyl 6-(*tert*-Butyl)(1*R,4*R**,6*S**)-6-(Methyl(phenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-5g).** According to **GP1**, *N*-Cbz-1,2-dihydropyridine (393 mg, 1.83 mmol) and *tert*-butyl 2-(diethylcarbamoyl)acrylate (**4g**, 321 mg, 1.23 mmol) were heated for 6 days. FC purification (*n*-hexane/Et_2O 1:1 → 3:7) afforded a mixture of diastereoiosmers ***endo*-5g**:***exo*-5g** in a 94:6 ratio (280 mg, 48%): Isolated ***endo*-5g**, colorless paste. ^1H NMR (DMSO-d_6, 400 MHz, 398 K): δ 7.44−7.13 (m, 10H), 6.44−6.34 (m, 2H), 5.35−5.28 (m, 1H), 5.15−5.05 (AB, m, 2H), 3.27−3.15 (m, 4H), 2.92−2.85 (m, 1H), 2.85−2.81 (m, 1H), 2.67 (*br.* d, J = 13.0 Hz, 1H), 1.63 (dt, J = 13.2, 2.9 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 169.0, 167.5, 154.0, 144.0, 136.5, 133.4, 130.5, 128.2, 127.5, 126.9, 126.6, 126.5, 126.0, 81.2, 65.5, 60.0, 49.0, 45.32, 38.3, 32.5, 29.8, 27.0. IR (neat): ν = 2976, 2936, 1694, 1600, 1495, 1443, 1413, 1367, 1272, 1251, 1153, 1110, 1085, 733, 697. HRMS (ES): m/z calcd for $C_{28}H_{33}N_2O_5$ 477.2389 $[M + H]^+$, found 477.2379. Isolated ***exo*-5g**, pale yellow paste. ^1H NMR (DMSO-d_6, 398 K, 400 MHz): δ 7.39−7.26 (m, 8H), 7.19−7.12 (m, 2H), 6.48 (ddd, J = 7.9, 5.8, 1.5 Hz, 1H), 6.31 (ddd, J = 7.9, 6.5, 1.2 Hz, 1H), 5.25 (dd, J = 5.8, 1.2 Hz, 1H), 5.11−4.99 (m, 2H), 3.26−3.22 (m, 1H), 3.11 (s, 3H), 2.92 (dt, J = 10.1, 2.7 Hz, 1H), 2.85−2.80 (m, 1H), 2.41 (dd, J = 12.9, 3.0 Hz, 1H), 1.66 (dt, J = 13.0, 2.7 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 168.9, 168.8, 153.8, 143.0, 136.2, 132.9, 131.5, 128.1, 127.4, 126.8, 126.6, 126.2, 125.9, 81.5, 65.4, 61.0, 51.1, 44.8, 37.0, 32.2, 29.7, 26.7. HRMS (ES): m/z calcd for $C_{28}H_{33}N_2O_5$ 477.2389 $[M + H]^+$, found 477.2386.

General Procedure for DA Reactions between α-Amido Acrylates and Cyclopentadiene (GP2). Cyclopentadiene (5 equiv) and α-amido acrylate (1 equiv) were transferred to a Biotage microwave vial containing a Teflon-coated magnetic stirrer bar which was subsequently thoroughly purged with Ar prior to sealing. The reaction was then heated at 80 °C until consumption of the dienophile was observed by TLC analysis. The reaction mixture was directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

Methyl (1*R,2*R**,4*R**)-2-(Diethylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-6a) and Methyl (1*R**,2*S**,4*R**)-2-(Diethylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-6a).** According to **GP2**, cyclopentadiene (0.23 mL, 2.8 mmol) and methyl 2-(diethylcarbamoyl)acrylate (**4a**, 102 mg, 0.55 mmol) were heated for 24 h. FC purification (Et_2O/*n*-hexane 3:2) afforded a mixture of diastereoisomers ***endo*-6a**:***exo*-6a** in a 78:22 ratio (62 mg, 45%). Isolated ***endo*-6a**, colorless paste. ^1H NMR (DMSO-d_6, 400 MHz): δ 6.29 (dd, J = 5.6, 2.9 Hz, 1H), 5.82 (dd, J = 5.7, 2.9 Hz, 1H), 3.57 (s, 3H), 3.46−3.41 (m, 1H), 3.39−3.31 (m, 1H), 3.30−3.20 (m, 1H), 3.18−3.05 (m, 2H), 2.92−2.79 (m, 1H), 2.13−1.97 (m, 1H), 1.70 (dd, J = 11.8, 3.4 Hz, 1H), 1.42−1.36 (m, 2H), 0.98 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 172.7, 169.7, 140.9, 132.6, 59.1, 52.6, 51.7, 50.4, 42.2, 40.5, 36.1, 13.4, 12.6. IR (neat): ν = 2974, 2941, 1733, 1642, 1456, 1432, 1274, 1251, 1236, 1116, 1059, 711. HRMS (ES): m/z calcd for $C_{14}H_{22}NO_3$ 252.1600 $[M + H]^+$, found 252.1594. ***Exo*-6a** not fully separated from ***endo*-6a**, colorless oil. Distinguishable peaks only: ^1H NMR (DMSO-d_6, 400 MHz): δ 6.14 (dd, J = 5.6, 3.0 Hz, 1H), 6.11−6.03 (m, 1H), 3.66 (s, 3H), 2.35−2.24 (m, 1H), 1.51 (d, J = 8.6 Hz, 1H), 1.31−1.26 (m, 1H). Distinguishable peaks only: ^{13}C NMR (DMSO-d_6, 101 MHz,) δ 174.6, 168.3, 138.0, 135.9, 61.0, 53.0, 51.0, 47.0, 37.6, 13.7, 12.4.

Methyl (1*R,2*R**,4*R**)-2-(Methyl(phenyl)carbamoyl)bicyclo-[2.2.1]hept-5-ene-2-carboxylate (*endo*-6b) and Methyl (1*R**,2*S**,4*R**)-2-(Methyl(phenyl)carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-6b).** According to **GP2**, cyclopentadiene (0.38 mL, 4.56 mmol) and methyl 2-(methyl(phenyl)carbamoyl)-acrylate (**4b**, 200 mg, 0.91 mmol) were heated for 5 h. FC purification (Et_2O: *n*-hexane 1:1 → 3:2) afforded a mixture of diastereoisomers ***endo*-6b**:***exo*-6b** in a 80:20 ratio (222 mg, 86%): Isolated ***endo*-6b**, yellow solid. Mp = 61−63 °C. ^1H NMR (DMSO-d_6, 373 K, 400 MHz): δ 7.41−7.34 (m, 2H), 7.32−7.25 (m, 1H), 7.21−7.13 (m, 2H), 6.19 (dd, J = 5.6, 3.0 Hz, 1H), 5.73 (dd, J = 5.7, 2.9 Hz, 1H), 3.47 (s, 3H), 3.43−3.39 (m, 1H), 3.16 (s, 3H), 2.88−2.82 (m, 1H), 1.98 (dd, J = 12.0, 3.6 Hz, 1H), 1.71 (dd, J = 11.9, 3.0 Hz, 1H), 1.60 (dt, J = 8.5, 1.6 Hz, 1H), 1.43−1.37 (m, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz, 398 K): δ 170.6, 170.3, 142.6, 139.5, 131.7, 128.4, 127.7, 126.8, 58.7, 51.4, 51.1, 49.3, 41.5, 38.3, 35.8. IR (neat): ν = 2974, 1737, 1648, 1595, 1496, 1357, 1251, 1231, 1116, 1057, 705. HRMS (ES): m/z calcd for $C_{17}H_{20}NO_3$ 286.1443 $[M + H]^+$, found 286.1468. ***Exo*-6b** not fully separated from ***endo*-6b**, colorless oil. Distinguishable peaks only: ^1H NMR (DMSO-d_6, 400 MHz, 373 K): δ 3.65 (s, 3H), 3.12 (s, 3H), 2.95−2.88 (m, 3H), 2.81−2.73 (m, 1H), 2.04 (dd, J = 12.0, 2.8 Hz, 1H), 1.88 (dd, J = 12.0, 3.6 Hz, 1H), 1.49 (d, J = 8.8 Hz, 1H), 1.27−1.21 (m, 1H). Distinguishable peaks only: ^{13}C NMR (DMSO-d_6, 101 MHz, 373 K): δ 172.9, 168.1, 137.6, 134.1, 128.5, 127.5, 126.8, 60.5, 51.5, 49.9, 46.6, 40.9, 38.4, 37.2, 30.0. From trace amounts of ***exo*-6b** isolated: HRMS (ES): m/z calcd for $C_{17}H_{20}NO_3$ 286.1443 $[M + H]^+$, found 286.1457.

Methyl (1*R,2*R**,4*R**)-2-(Diphenylcarbamoyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (*endo*-6c) and Methyl (1*R**,2*S**,4*R**)-2-(Diphenylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-6c).** According to **GP2**, cyclopentadiene (0.30 mL, 3.56 mmol) and methyl 2-(diphenylcarbamoyl)acrylate (**4c**, 200 mg, 0.71 mmol) were heated for 80 min. FC purification (*n*-hexane/Et_2O 7:3 → 3:7) afforded a mixture of diastereoisomers ***endo*-6c**:***exo*-6c** in a 70:30 ratio (221 mg, 90%). Isolated ***endo*-6c**, colorless paste. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.46−7.16 (m, 10H), 6.16 (dd, J = 5.6, 2.9 Hz, 1H), 5.68 (dd, J = 5.7, 2.9 Hz, 1H), 3.43 (s, 3H), 3.39−3.36 (m, 1H), 2.90−2.78 (m, 1H), 2.18 (dd, J = 12.0, 3.6 Hz, 1H), 1.64 (d, J = 8.3 Hz, 1H), 1.47 (dd, J = 11.9, 2.8 Hz, 1H), 1.43−1.37 (m, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 171.7, 171.0, 140.7, 132.5, 129.5, 127.9, 59.7, 52.8, 52.4, 50.5, 42.59, 37.1. IR (neat): ν = 2980, 2948, 1743, 1714, 1663, 1491, 1333, 1298, 1273, 1255, 1232, 1154, 1116, 756, 700. HRMS (ES): m/z calcd for $C_{22}H_{22}NO_3$ 348.1600 $[M + H]^+$, found 348.1606. ***Exo*-6c** not fully separated from ***endo*-6c**, colorless paste. Distinguishable peaks only: ^1H NMR (DMSO-d_6, 400 MHz): δ 6.36 (dd, J = 5.6, 2.8 Hz, 1H), 6.27 (dd, J = 5.6, 2.9 Hz, 1H), 3.69 (s, 3H), 2.80−2.70 (m, 2H), 1.72 (dd, J = 12.1, 3.5 Hz, 1H). Distinguishable peaks only: ^{13}C NMR (DMSO-d_6, 101 MHz): δ 173.8, 169.2, 139.3, 134.5, 61.7, 52.9, 48.2, 41.8, 38.6. From trace amounts of ***exo*-6c** isolated: HRMS (ES): m/z calcd for $C_{22}H_{22}NO_3$ 348.1600 $[M + H]^+$, found 348.1591.

Methyl (1*R,2*R**,4*R**)-2-((2-Isobutoxy-6-isobutylphenyl)-carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-6d) and Methyl (1*R**,2*S**,4*R**)-2-((2-isobutoxy-6-isobutylphenyl)-carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-6d).** According to **GP2**, cyclopentadiene (0.10 mL, 1.19 mmol) and methyl 2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)acrylate (**4d**, 30 mg, 0.09 mmol) were heated for 14 h. FC purification (*n*-hexane/Et_2O 9:1 → 4:1) afforded a mixture of diastereoisomers ***endo*-6d**:***exo*-6d** in a 84:16 ratio (28 mg, 58%). Isolated ***endo*-6d**, white solid. Mp = 62.0 °C. ^1H NMR (DMSO-d_6, 400 MHz): δ 8.76 (s, 1H), 7.14 (t, J = 7.9 Hz, 1H), 6.82 (dd, J = 8.3, 1.2 Hz, 1H), 6.73 (dd, J = 7.7, 1.2 Hz, 1H), 6.29 (dd, J = 5.6, 2.9 Hz, 1H), 5.99 (dd, J = 5.6, 2.8 Hz, 1H), 3.65 (d, J = 6.4 Hz, 2H), 3.62 (s, 3H), 3.59−3.54 (m, 1H), 2.93−2.81 (m, 1H), 2.36 (dd, J = 12.3, 3.7 Hz, 1H), 2.33−2.23 (m, 2H), 2.00−1.86 (m, 2H), 1.82−1.68 (m, 1H), 1.50 (d, J = 8.4 Hz, 1H), 1.46−1.38 (m, 1H), 0.95 (dd, J = 6.6, 2.2 Hz, 6H), 0.80 (dd, J = 6.5, 3.9 Hz, 6H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 172.3, 169.3, 155.4, 141.0, 140.4, 133.9, 127.7, 125.2, 122.1, 110.0, 74.4, 62.0, 52.6, 49.5, 48.9, 28.6, 28.4, 23.0, 22.9, 19.5. IR (neat): ν = 3364, 2955, 2928, 2868, 1732, 1762, 1586, 1498, 1461, 1276, 1260, 1054, 750. HRMS (ES): m/z calcd for $C_{24}H_{34}NO_4$ 400.2488 $[M + H]^+$, found 400.2477. Isolated ***exo*-6d**, white solid. Mp = 100.3 °C. ^1H NMR (DMSO-d_6, 400 MHz): δ 8.65 (s, 1H), 7.12 (t, J = 7.9 Hz, 1H), 6.79 (dd, J = 8.5, 1.2 Hz, 1H), 6.76−6.69 (m, 1H), 6.27−6.09 (m, 2H), 3.70 (s, 3H), 3.68−3.58 (m, 3H), 2.85 (s, 1H), 2.28−2.21 (m, 2H), 2.17 (dd, J = 12.5, 3.5 Hz, 1H), 2.05−1.91 (m, 2H), 1.87−1.70 (m, 1H), 1.47−1.37 (m, 2H), 0.96 (dd, J = 9.0, 6.6 Hz, 6H), 0.79 (dd, J = 6.4, 1.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 173.7, 167.9, 155.3, 141.0, 139.1, 134.6, 127.5, 125.2, 121.9, 110.0, 74.6, 62.2, 52.9, 49.3, 48.9, 41.9, 35.7, 28.3, 28.2, 23.0, 19.7. IR (neat): ν = 3332, 2955, 2928, 2868, 1733, 1704, 1500, 1462, 1276, 1261, 1056, 750. HRMS (ES): m/z calcd for $C_{24}H_{34}NO_4$ 400.2488 $[M + H]^+$, found 400.2497.

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Methyl (1*R,2*R**,4*R**)-2-((2,6-Diisopropylphenyl)-carbamoyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-6e) and Methyl (1*R**,2*S**,4*R**)-2-((2,6-Diisopropylphenyl)-carbamoyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (*exo*-6e).** According to **GP2**, cyclopentadiene (0.20 mL, 2.40 mmol) and methyl 2-((2,6-diisopropylphenyl)carbamoyl)acrylate (**4e**, 139 mg, 0.48 mmol) were heated for 2 h, after which dry toluene (0.2 mL) was added to aid solubility, and the mixture was heated at 80 °C for a further 30 min. FC purification (*n*-hexane/Et_2O 4:1 → 3:2) afforded a mixture of diastereoisomers ***endo*-6e**:***exo*-6e** in a 76:24 ratio (153 mg, 90%). Isolated ***endo*-6e**, white powder. Mp = 140−142 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.20 (s, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.17−7.09 (m, 2H), 6.31 (dd, J = 5.7, 2.9 Hz, 1H), 6.02 (dd, J = 5.8, 2.9 Hz, 1H), 3.71−3.56 (m, 4H), 3.05−2.86 (m, 3H), 2.32 (dd, J = 12.3, 3.6 Hz, 1H), 1.94 (dd, J = 12.2, 2.7 Hz, 1H), 1.52−1.42 (m, 1H), 1.43−1.33 (m, 1H), 1.24−0.94 (m, 12H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 172.2, 169.9, 146.6, 140.3, 133.8, 133.1, 128.1, 123.2, 62.1, 52.5, 49.3, 49.0, 35.8, 28.3, 28.3, 23.9, 23.8, 23.7. IR (neat): ν = 3311, 2960, 2932, 2868, 1743, 1644, 1501, 1236, 1157, 735. HRMS (ES): m/z calcd for $C_{22}H_{30}NO_3$ 356.2226 [M + H]$^+$, found 356.2224. Isolated ***exo*-6e**, white powder. Mp = 165 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.03 (s, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.15−7.06 (m, 2H), 6.30 (dd, J = 5.7, 3.0 Hz, 1H), 6.09 (dd, J = 5.5, 2.9 Hz, 1H), 3.71 (s, 3H), 3.67−3.61 (m, 1H), 3.08−2.95 (m, 1H), 2.93−2.82 (m, 2H), 2.20 (dd, J = 12.5, 3.7 Hz, 1H), 2.02 (d, J = 12.3 Hz, 1H), 1.50−1.42 (m, 2H), 1.21−0.96 (m, 12H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 173.8, 168.8, 146.8, 146.7, 139.6, 134.3, 133.1, 128.0, 123.2, 62.3, 52.8, 49.2, 49.1, 41.9, 35.7, 28.0, 24.0, 23.9. IR (neat): ν = 3300, 2957, 2928, 2868, 1738, 1639, 1504, 1236, 736. HRMS (ES): m/z calcd for $C_{22}H_{30}NO_3$ 356.2226 [M + H]$^+$, found 356.2236.

tert*-Butyl (1*R**,2*R**,4*R**)-2-(Diethylcarbamoyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (*endo*-6f) and *tert*-Butyl (1*R**,2*S**,4*R**)-2-(Diethylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-6f).** According to **GP2**, cyclopentadiene (0.28 mL, 3.30 mmol) and *tert*-butyl 2-(diethylcarbamoyl)acrylate (**4f**, 150 mg, 0.66 mmol) were heated for 48 h. FC purification (*n*-hexane/Et_2O 4:1 → 2:3) afforded a mixture of diastereoisomers ***endo*-6f**:exo*-6f** in a 83:17 ratio (106 mg, 55%). Isolated ***endo*-6f**, white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.29 (dd, J = 5.7, 2.9 Hz, 1H), 5.85 (dd, J = 5.7, 2.9 Hz, 1H), 3.52−3.39 (m, 2H), 3.31−3.21 (m, 1H), 3.19−3.01 (m, 2H), 2.83 (*br.* s, 1H), 1.95 (dd, J = 11.6, 2.1 Hz, 1H), 1.67 (dd, J = 11.8, 3.6 Hz, 1H), 1.43−1.28 (m, 11H), 1.01 (dt, J = 17.9, 7.0 Hz, 6H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 171.0, 170.2, 140.6, 132.6, 81.0, 60.0, 51.85, 50.5, 42.3, 39.1, 35.6, 28.0, 13.6, 12.4. IR (neat): ν = 2976, 2948, 1718, 1635, 1458, 1423, 1367, 1280, 1257, 1139, 1116, 1100, 1052, 845, 709. HRMS (ES): m/z calcd for $C_{17}H_{28}NO_3$ 294.2069 [M + H]$^+$, found 294.2065. ***Exo*-6f** not fully separated from ***endo*-6f**, white powder. Distinguishable peaks only: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.16−6.10 (m, 1H), 6.09−6.02 (m, 1H). Distinguishable peaks only: ^{13}C NMR (DMSO-d_6, 101 MHz): δ 81.4, 41.9, 37.2, 27.9, 13.9, 12.0. From trace amounts of ***exo*-6f** isolated: IR (neat): ν = 2976, 2944, 1718, 1636, 1458, 1421, 1367, 1280, 1257, 1139, 1117, 1099, 1053, 846, 709. HRMS (ES): m/z calcd for $C_{17}H_{28}NO_3$ 294.2069 [M + H]$^+$, found 294.2057.

tert*-Butyl (1*R**,2*R**,4*R**)-2-(Methyl(phenyl)carbamoyl)-bicyclo-[2.2.1]hept-5-ene-2-carboxylate (*endo*-6g) and *tert*-Butyl (1*R**,2*S**,4*R**)-2-(Methyl(phenyl)carbamoyl)bicyclo-[2.2.1]hept-5-ene-2-carboxylate (*exo*-6g).** According to **GP2**, cyclopentadiene (0.42 mL, 4.94 mmol) and *tert*-butyl 2-(diethyl-carbamoyl)acrylate (**4g**, 258 mg, 0.99 mmol) were heated for 24 h. FC purification (*n*-hexane/Et_2O 4:1 → 1:1) afforded a mixture of diastereoisomers ***endo*-6g**:exo*-6g** in a 81:19 ratio (217 mg, 67%). Isolated ***endo*-6g**, off-white powder. Mp = 132−136 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.39 (t, J = 7.7 Hz, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.24−7.18 (m, 2H), 6.40−6.20 (*br.* m, 1H), 5.85 (*br.* M, 1H), 3.44−3.38 (m, 1H), 3.14 (s, 3H), 2.87 (*br.* s, 1H), 2.09−1.81 (*br.* m, 1H), 1.50−1.33 (m, 11H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 171.3, 170.5, 140.6, 132.4, 129.4, 127.0, 81.3, 60.2, 52.0, 50.6, 42.6, 38.7, 35.7, 28.1. IR (neat): ν = 2976, 2932, 1731, 1660, 1494, 1366, 1257, 1154, 1115, 764. HRMS (ES): m/z calcd for $C_{20}H_{26}NO_3$ 328.1906 [M + H]$^+$, found 328.1913. ***Exo*-6g** not fully separated from ***endo*-6g**, white powder. Distinguishable peaks only: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.22−6.03 (m, 2H). Distinguishable peaks only: ^{13}C NMR (DMSO-d_6, 101 MHz): δ 172.8, 129.5, 81.6, 28.0. From trace amounts of ***exo*-6g** isolated: IR (neat): ν = 2981, 1721, 1658, 1494, 1367, 1247, 1154, 1075, 693. HRMS (ES): m/z calcd for $C_{20}H_{26}NO_3$ 328.1906 [M + H]$^+$, found 328.1909.

General Procedure for DA Reactions between α-Amido Acrylates 4e and 4f and Cyclopentadiene in the Presence of Et_2AlCl. To a solution of α-amido acrylate (**4e** or **4f**, 1 equiv) in dry CH_2Cl_2 (0.1 M) at 0 °C under Ar was added Et_2AlCl (1 equiv, 1 M in hexane). The reaction mixture was stirred at rt for 30 min before cooling back down to 0 °C and the addition of cyclopentadiene (10 equiv), after which the reaction mixture was stirred at rt until consumption of the dienophile was observed by TLC analysis. The reaction mixture was then directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

General Procedure for DA Reactions between α-Amido Acrylates 4e and 4f and Cyclopentadiene in the Presence of $B(C_6F_5)_3$. To a solution $B(C_6F_5)_3$ (1 equiv) and 4 Å MS in dry CH_2Cl_2 at rt under Ar was added a solution of α-amido acrylate (**4e** or **4f**, 1 equiv) in dry CH_2Cl_2 (0.1M). The reaction mixture was stirred at rt for 30 min before cooling back down to 0 °C and the addition of cyclopentadiene (10 equiv), after which the reaction mixture was stirred at rt until consumption of the dienophile was observed by TLC analysis. The reaction mixture was then directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

General Procedure for DA Reactions between α-Amido Acrylates 4e and 4f and Cyclopentadiene in the Presence of TBSOTf. To a solution of α-amido acrylate (**4e** or **4f**, 1 equiv) in dry CH_2Cl_2 (0.1M) at 0 °C under Ar was added freshly distilled TBSOTf (1 equiv). The reaction mixture was stirred at rt for 30 min before cooling back down to 0 °C and addition of cyclopentadiene (10 equiv), after which the reaction mixture was stirred until consumption of the dienophile was observed by TLC analysis. The reaction mixture was then directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01684.

^{1}H and ^{13}C NMR for all new compounds (PDF)

Crystallographic details for compound **2** (CIF)

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Notes

The authors declare no competing financial interest.

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