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New conjugated dienamides via palladium-catalyzed selective aminocarbonylation of enynes

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ABSTRACT

New conjugated dienamides have been synthesized effectively via palladium-catalyzed aminocarbonylation of enynes in the presence of various amines, diaminoalkanes, and aminoalcohols. The products have been utilized as substrates in alkoxycarbonylation reactions using methanol as the nucleophile and $Pd(PPh_3)_2Cl_2$ as the catalyst to afford novel ω-amidoesters in high yields and selectivities. Interestingly, the product obtained from the alkoxycarbonylation reaction of the dienamide product of enyne **1b** was observed to undergo carbonylation of the α,β-double bond with respect to the carbonyl group and isomerization of the second isolated double bond.

Dienamides are recognized as key reactive intermediates in organic synthesis due to their synthetic potential and occurrence in Nature.[1] A variety of dienamide derivatives have been isolated from natural sources and have been reported to have antioxidant and cytotoxic activities.[2] Several alkaloids have been synthesized using dienamides as starting materials.[3] Acyclic dienamides are also key constituents in a number of biologically active natural products and pharmaceutically relevant units.[4] Despite their utility and biological potential, available synthetic routes for dienamides are still very limited.[5] Moreover, reports on the synthesis of dienamides via metal-catalyzed carbonylation are rare in the literature. Imanda and Alper reported the palladium-catalyzed regioselective carbonylation of propargyl amines into 2,4- or 2,3-dienamides.[6] The need to develop efficient, mild and simple methods for the synthesis of more versatile and new dienamides remains an interesting challenge. Aminocarbonylation of enynes can be considered as an attractive route toward the simple, efficient and practical preparation of a variety of dienamides. Encouraged by the importance of aminocarbonylation reactions in organic syntheses,[7] our group has succeeded in the development of different palladium catalyst systems for the aminocarbonylation of various internal and terminal alkyl and aromatic alkynes, using different types of amines as nucleophiles.[8]

In this Letter, we report a one-step protocol for the regioselective synthesis of new dienamides, in high yields, via palladium-catalyzed aminocarbonylation of enyne substrates using a modified catalytic system that we reported previously for the aminocarbonylation of terminal alkynes.[8a] Different reaction parameters have been screened and optimized in order to maximize the yield and the regioselectivity of the aminocarbonylation. Moreover, the dienamides obtained from the aminocarbonylation step were subjected to further catalytic alkoxycarbonylation with methanol to produce new ω-amidoesters with interesting structural properties.

The aminocarbonylation of 1-ethynylcyclohexene (**1a**), adopted as a model substrate, with diisobutylamine (**2a**) in the presence of a palladium-diphosphine catalyst system was carefully optimized by varying the reaction conditions (Eq. (1)) and the results are summarized in Table 1. Excellent conversion and regioselectivity toward the (2-*gem*)-4-dienamide **3aa** was achieved, while (2-*trans*)-4-dienamide **4aa** was obtained as a minor product. The use of 1,3-bis(diphenylphosphino)propane (dppp) as the ligand (Table 1, entry 2) led to a higher conversion of **1a** and excellent selectivity toward **3aa**, and better reproducibility compared to 1,4-bis(diphenylphosphino)butane (dppb) (Table 1, entry 1), 1,1'-bis(diphenylphosphino)ferrocene (dppf) (Table 1, entry 3), and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (Table 1, entry 4) as ligands and $Pd(OAc)_2$ as the catalyst precursor. Low to average conversions (12% and 48%) were obtained with the monophosphine ligands PPh_3 and $P(p\text{-Tol})_3$ (Table 1, entries 12 and 13), respectively. The major carbonylation product of the reaction with

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Table 1
Selected experimental results for the optimization of the catalyst system for the aminocarbonylation of **1a**[a]

Entry	Catalyst precursor	Ligand	Conversion of **1a**[b] (%)	Product distribution[b] (%)		**1′a**[b] (%)
				3aa	**4aa**	
1	$Pd(OAc)_2$	dppb	92	93	5	2
2	$Pd(OAc)_2$	dppp	98	94	4	2
3	$Pd(OAc)_2$	dppf	92	82	12	6
4	$Pd(OAc)_2$	BINAP	83	88	9	3
5	$PdSO_4$	dppp	97	93	4	3
6	$PdCl_2(PPh_3)_2$	dppp	80	92	1	7
7	$Pd(NO_3)_2$	dppp	100	94	5	1
8[c]	$Pd(OAc)_2$	dppp	65	84	4	12
9[d]	$Pd(OAc)_2$	dppp	86	85	6	9
10[e]	$Pd(OAc)_2$	dppp	78	72	6	22
11[f]	$Pd(OAc)_2$	—	50	—	—	100
12	$Pd(OAc)_2$	PPh_3	20	49	3	48
13	$Pd(OAc)_2$	P(*p*-Tol)$_3$	48	42	13	45

[a] Reaction conditions: catalyst precursor (0.02 mmol), ligand (0.08 mmol), 1-ethynylcyclohexene (**1a**) (2 mmol), diisobutylamine (**2a**) (2.2 mmol), *p*-TsOH (0.3 mmol), CO (200 psi), CH_3CN (10 ml), 110 °C, 6 h.
[b] Determined by GC based on **1a**.
[c] Solvent = CH_2Cl_2.
[d] Temperature = 90 °C.
[e] No *p*-TsOH was added.
[f] No ligand was added.

PPh_3 and P(*p*-Tol)$_3$ was **3aa** (49% and 42%, respectively) in addition to the homocoupling product (48% and 45%, respectively). It is clear that the mechanism of the carbonylation reaction of enynes using monosphosphine ligands differs from that occurring in the presence of diphosphines.[9]

Comparable activities and selectivities were obtained in the aminocarbonylation of **1a** when dppp was applied with other palladium(II) precursors (Table 1, entries 5–7). The use of CH_2Cl_2 as the solvent or a lower temperature of 90 °C resulted in a decrease in both the activity and selectivity of the aminocarbonylation reaction of **1a** (Table 1, entries 8 and 9). The catalyst system still showed good activity in the aminocarbonylation of **1a** even in the absence of *p*-TsOH as an additive (Table 1, entry 10). However, the absence of the ligand resulted only in the formation of the product **1′a** obtained via homocoupling of **1a**, and no carbonylation products were identified (Table 1, entry 11). Furthermore, no polymerization by-products of **1a** were identified from any of the experiments.

We next investigated the aminocarbonylation of **1a** with a range of primary and secondary amines and the results are summarized in Table 2. Excellent conversions (82–98%) and selectivities (94–99%) were achieved with alkyl amines **2a–d** (Table 2, entries 1–4) and benzylamine **2e** (Table 2, entry 5) yielding the corresponding (2-*gem*)-4-dienamide isomers **3aa–ae** as the predominant products. Surprisingly, no catalytic activity was observed in the presence of aromatic amines such as aniline **2f** and naphthylamine **2g** (Table 2, entries 6 and 7), probably due to the low nucleophilicity of these nucleophiles.

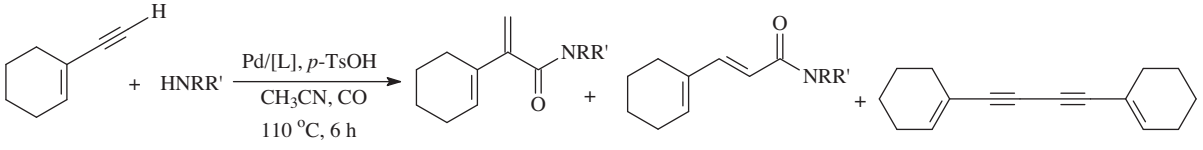
These interesting results have encouraged us to initiate a separate computational mechanistic study to clarify the possible catalytic pathways for the aminocarbonylation of these enynes, and also to compare them with our previously reported mechanistic study for the aminocarbonylation of terminal alkynes.[9]

The palladium-catalyzed aminocarbonylation reaction was also successfully applied for the carbonylation of **1a** in the presence of diaminoalkanes **5a–c** (Scheme 1). Interestingly, the two amino groups in the diaminoalkanes, regardless of the number of carbon atoms in the chain, were reactive as amines in the aminocarbonylation of two molecules of **1a** leading to the formation of new alkyl-di-(2-*gem*)-4-dienamides **6aa–ac** in excellent isolated yields (81–91%).

It is worth noting that the catalyst system composed of $Pd(OAc)_2$ and dppp was also active and selective in the aminocarbonylation of 2-methyl-1-buten-3-yne (**1b**) using the amines **2a**, **2h**, and 1,3-propanediamine (**5a**) as nucleophiles.[10] Excellent isolated yields (78–95%) of dienamides **3ba**, **3bh**, and **6ba** were obtained (Scheme 2).

The most interesting results were obtained when we utilized the described catalyst system [$Pd(OAc)_2$/dppp] for the aminocarbonylation of enyne **1a** with aminoalcohols **7a–c** as nucleophiles. These are considered as interesting molecules having two different functionalities that are typically available as nucleophiles for aminocarbonylation as well as alkoxycarbonylation reactions. Surprisingly, aminocarbonylation products were obtained exclusively (Scheme 3), and the OH function remained intact. This result was confirmed by the absence of any catalytic activity for our aminocarbonylation catalyst system in the alkoxycarbonylation reaction of **1a** with different alcohols. It is important to note that new dienamides **8aa–ac**, having diene, amine, and hydroxy functions are important for the synthesis of new and useful heterocyclic compounds.

The presence of the interesting diene functionality in the products of the aminocarbonylation of enynes encouraged us to consider the obtained dienamides as substrates for alkoxycarbonylation

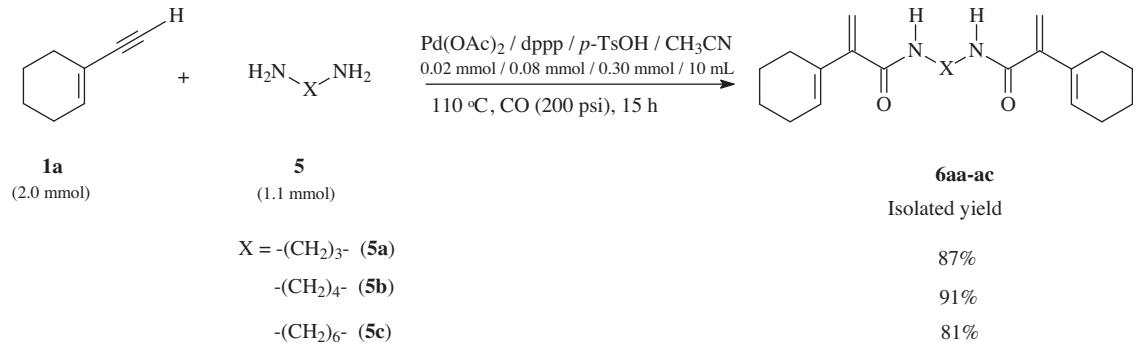


1a **2a** [R=R'=$CH_2CH(CH_3)_2$] **2b** [R=$CH(CH_3)_2$; R'=H] **2c** [R=R'=$CH(CH_3)_2$] **2d** [R=$CH_2(CH_2)_4CH_3$; R'=H] **2e** [R=$CH_2C_6H_5$; R'=H] **2f** [R=C_6H_5; R'=H] **2g** [R=$C_{10}H_7$; R'=H] **3aa-ae** **4aa-ae** **1'a** (1)

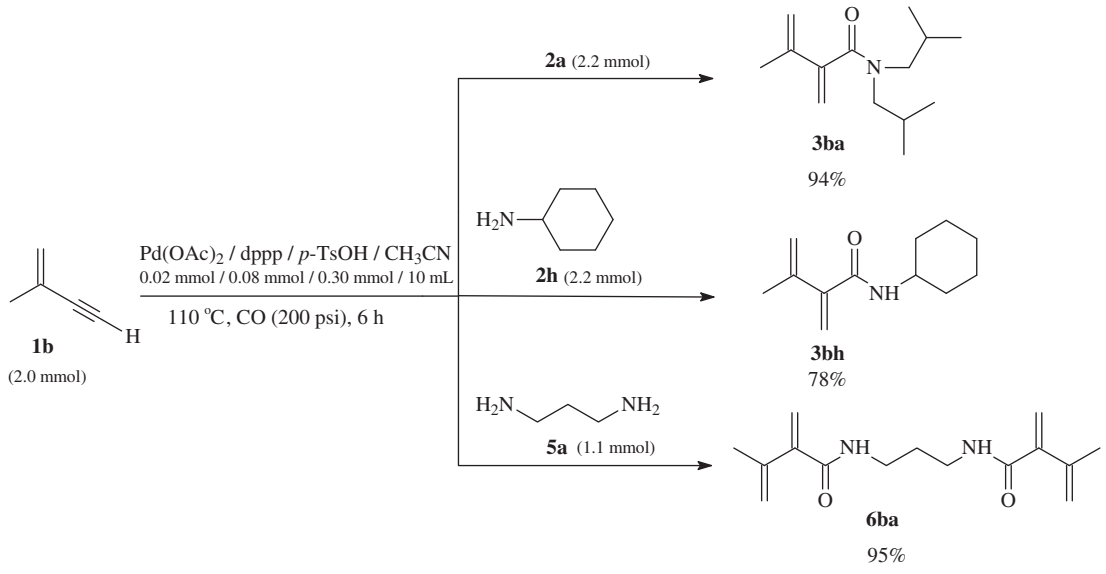
Table 2
Pd(II)-catalyzed aminocarbonylation of **1a** in the presence of amines **2a–g**[a]

Entry	Amine	Conversion (%)[b]	Product distribution[b] (%)		
			3 [ ][c]	**4**	**1′a**
1	Diisobutylamine (**2a**)	98	**3aa** 95 [93]	**4aa** 3	2
2	Isopropylamine (**2b**)	91	**3ab** 97 [84]	**4ab** 3	0
3	Diisopropylamine (**2c**)	93	**3ac** 89 [85]	**4ac** 5	6
4	Hexylamine (**2d**)	96	**3ad** 99 [90]	**4ad** 1	0
5	Benzylamine (**2e**)	82	**3ae** 98 [81]	**4ae** 1	1
6	Aniline (**2f**)	0	—	—	
7	Naphthylamine (**2g**)	0	—	—	

[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppp (0.08 mmol), 1-ethynylcyclohexene (**1a**) (2 mmol), amine (2.2 mmol), *p*-TsOH (0.3 mmol), CO (200 psi), CH_3CN (10 ml), 110 °C, 6 h.
[b] Determined by GC based on **1a**.
[c] Isolated yield.

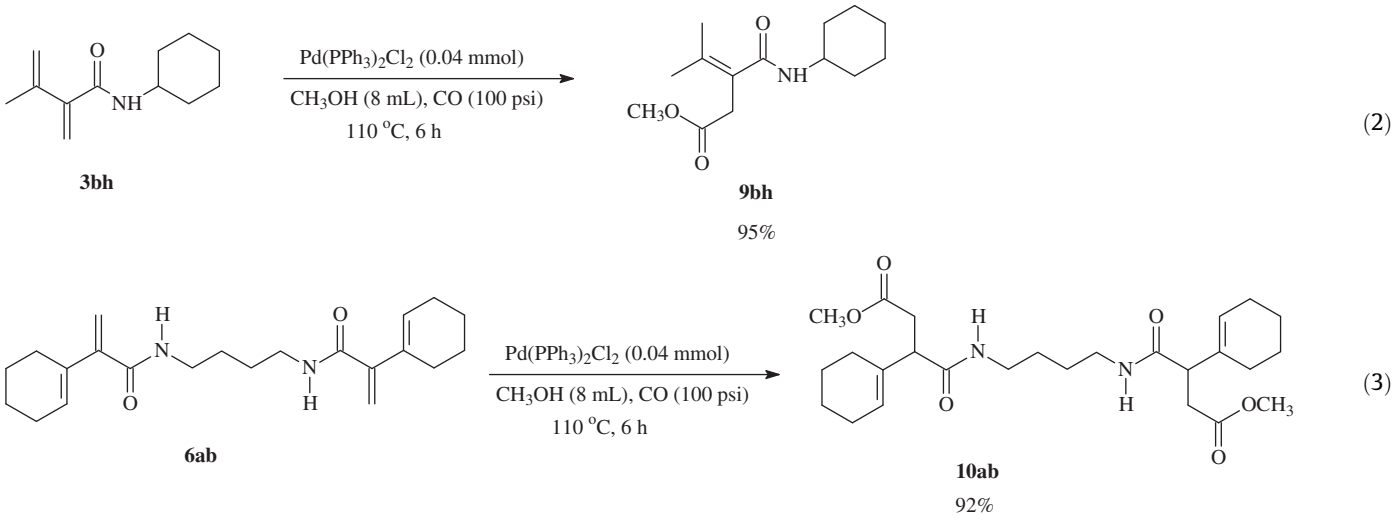


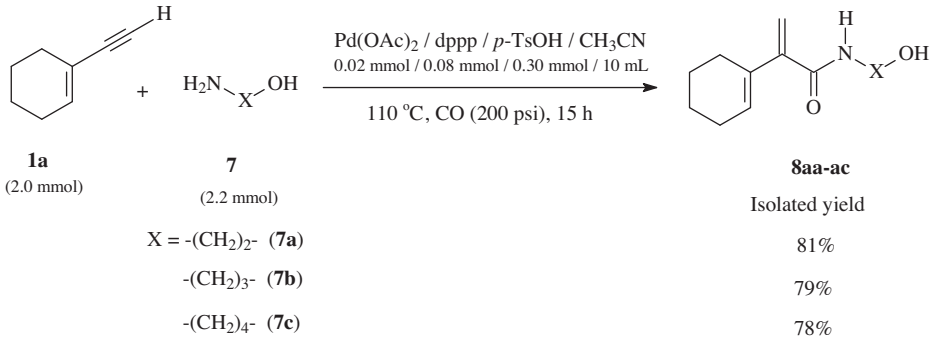
Scheme 1. Aminocarbonylation of enyne **1a** using diamines **5a–c**.



Scheme 2. Aminocarbonylation of enyne **1b** using amines **2a**, **2h**, and **5a**.

reactions with methanol using $Pd(PPh_3)_2Cl_2$ as the catalyst.[11] To our delight, the reactions proceeded smoothly to yield the required alkoxycarbonylation products in excellent isolated yields (92–95%). Interestingly, the alkoxycarbonylation of dienamide **3bh** proceeded with isomerization of the second isolated double bond. This isomerization behavior was not observed for the isolated double bonds located in the cyclic moiety of substrate **6ab** (Eqs. 2 and 3).[12]





Scheme 3. Aminocarbonylation of enyne **1a** using aminoalcohols **7a–c**.

In conclusion, an efficient palladium-diphosphine catalyst system was applied for the aminocarbonylation of enyne substrates using various mono and diaminoalkanes, and aminoalcohols. The catalyst system showed excellent regioselectivity to produce (2-*gem*)-4-dienamide as the predominant product. Interesting and novel ω-amidoesters were obtained through the palladium-catalyzed alkoxycarbonylation of the dienamides prepared in this study.[13] A computational study of plausible mechanisms for the above noted reactions is in progress.

Acknowledgment

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10. General Procedure for the aminocarbonylation of enynes; A mixture of $Pd(OAc)_2$ (0.02 mmol), dppp (0.08 mmol), *p*-TsOH (0.3 mmol), enyne (2.0 mmol) and amine (2.2 mmol) or aminoalcohol (2.2 mmol) or diamine (1.1 mmol) in CH_3CN (10 ml) was placed in a glass liner, equipped with a stirrer bar, and then placed in a 45 ml Parr autoclave. The autoclave was vented three times with CO and then pressurized at room temperature with CO (200 psi). The mixture was stirred and heated at 110 °C for 6 h or 15 h. After cooling, the pressure was released, and the solid products were filtered and washed with methanol and dried under vacuum. The products were identified by ^1H and ^{13}C NMR, and FT-IR spectroscopy and EI-MS analyses.
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12. General Procedure for the alkoxycarbonylation of dienamides. A mixture of $Pd(PPh_3)_2Cl_2$ (0.04 mmol) and dienamide (0.5 mmol) in MeOH (8 ml) was placed in a glass liner, equipped with a stirring bar, and placed in a 45 ml Parr autoclave. The autoclave was vented three times with CO and then pressurized at room temperature with CO (100 psi). The mixture was stirred and heated at 110 °C for 6 h. After cooling, the pressure was released, the reaction mixture was filtered after adding anhydrous Na_2SO_4 and a sample of the filtrate was immediately analyzed by GC and GC–MS. The solvent was removed and the products were separated by preparative TLC (30% EtOAc/petroleum ether, 40–70 °C).
13. *Spectral data for representative compounds.* 2-Cyclohexenyl-*N*,*N*-diisobutylacrylamide (**3aa**): Oil, IR (CH_2Cl_2) υ (cm^{-1}) 1621 (CO), ^1H NMR δ (ppm) (500 MHz, $CDCl_3$): 0.79 [d, 6H, $CH(CH_3)_2$, J = 5.0 Hz], 0.80 [d, 6H, $CH(CH_3)_2$, J = 5.0 Hz], 1.55–1.57 [m, 4H, cyclohexenyl], 1.66–1.68 [m, 1H, $CH(CH_3)_2$], 1.87–1.89 [m, 1H, $CH(CH_3)_2$], 2.08–2.10 [m, 4H, cyclohexenyl], 2.97 (d, 2H, NCH_2 of isobutyl group, J = 7.5 Hz), 3.26 (d, 2H, NCH_2 of isobutyl group, J = 7.5 Hz), 4.92 (s, 1Hα, $=CH_2$), 5.15 (s, 1H$_\beta$, $=CH_2$), 5.80–5.83 (m, 1H, *CH*, cyclohexenyl); ^{13}C NMR δ (ppm) (125 MHz, $CDCl_3$), 20.0 $(CH_3)_2$, 20.3 $(CH_3)_2$,

21.9 [CH_2, cyclohexenyl], 22.4 [CH_2, cyclohexenyl], 24.4 (CH), 25.7 (CH), 25.8 [CH_2, cyclohexenyl], 28.7 [CH_2, cyclohexenyl], 50.6 (NCH_2 of isobutyl group), 55.6 (NCH_2 of isobutyl group), 109.9 (C CH_2 attached to cyclohexenyl), 129.1 (CH, cyclohexenyl), 138.1 (C, cyclohexenyl), 147.6 (*C* CH_2 attached to cyclohexenyl), 172.2 (CO); GC–MS *m*/*z* 264 (M+1). Anal. Calcd for $C_{17}H_{29}NO$ (263.42): C, 77.51; H, 11.10; N, 5.32. Found: C, 77.42; H, 11.07; N, 5.57.

N,*N*-(Propane-1,3-diyl)bis(2-cyclohexenyl)acrylamide (**6aa**): Oil, IR (CH_2Cl_2) υ (cm^{-1}) 1649 (CO), 3381 (NH); ^1H NMR δ (ppm) (500 MHz, $CDCl_3$): 1.51–1.54 [m, 2H], 1.63–1.65 [m, 8H cyclohexenyl], 2.06–2.07 [m, 8H, (cyclohexenyl)], 3.30 [q, 4H, *J* = 5.19 Hz], 5.15 (s, 2Hα, $=CH_2$), 5.27 (s, 2H$_\beta$, $=CH_2$), 5.88–5.91 (m, 2H, *CH*, cyclohexenyl), 6.67 [br s, 2H (NH)]; ^{13}C NMR δ (ppm) (125 MHz, $CDCl_3$), 21.7 [CH_2, cyclohexenyl], 22.3 [CH_2, cyclohexenyl], 25.6 [$(CH_2)_2$, cyclohexenyl], 29.7 (NCH_2CH_2), 35.8 ($(NCH_2)_2$), 113.1 (C CH_2 attached to cyclohexenyl), 129.2 (CH, cyclohexenyl), 133.0 (C, cyclohexenyl), 147.5 (*C* CH_2 attached to cyclohexenyl), 170.4 (CO); GC–MS *m*/*z* 343 (M+1). Anal. Calcd for $C_{21}H_{30}N_2O_2$ (342.48): C, 73.65; H, 8.83; N, 8.18. Found: C, 73.52; H, 8.77; N, 8.32.

2-Cyclohexenyl-*N*-(2-hydroxyethyl)acrylamide (**8aa**): Oil, IR (CH_2Cl_2) υ (cm^{-1}) 1658 (CO), 3354 (NH); ^1H NMR δ (ppm) (500 MHz, $CDCl_3$): 1.54–1.56 [m, 4H, cyclohexenyl], 2.07–2.10 [m, 4H cyclohexenyl], 3.43 (q, 2H, NCH_2, *J* = 6.10 Hz), 3.69 (q, 2H, OCH_2, *J* = 5.50 Hz), 4.4 (br s, 1H, OH), 5.18 (s, 1Hα, $=CH_2$), 5.32 (s, 1H$_\beta$, $=CH_2$), 5.92–5.94 (m, 1H, *CH*, cyclohexenyl), 6.45 [br s, 1H (NH)]; ^{13}C NMR δ (ppm) (125 MHz, $CDCl_3$), 21.8 (CH_2, cyclohexenyl), 22.4 (CH_2, cyclohexenyl), 25.6 (CH_2, cyclohexenyl) 25.7 (CH_2, cyclohexenyl), 42.4 (NCH_2), 61.9 (OCH_2), 113.6 (C CH_2 attached to cyclohexenyl), 129.5 (CH, cyclohexenyl), 133.0 (C, cyclohexenyl), 147.3 (*C* CH_2 attached to cyclohexenyl), 170.8 (CO); GC–MS *m*/*z* 196 (M+1). Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17. Found: C, 67.69; H, 8.47; N, 8.56.

Dimethyl-4,4′-butane-1,4-diylbisazanediylbis-3-cyclohexenyl-4-oxobutanoate (**10ab**): Oil, IR (CH_2Cl_2) υ (cm^{-1}) 1664 (CO), 3316 (NH); ^1H NMR δ (ppm) (500 MHz, $CDCl_3$): 1.47–1.49 (m, 8H), 1.97–2.07 (m, 8H), 2.11–2.14 (m, 4H), 2.89–2.92 (m, 4H), 3.26 [q, 4H, *J* = 5.5 Hz], 3.62 (s, 6H), 5.60–5.63 (m, 2H, *CH*), 5.85–5.87 (m, 2H, *CH*), 5.93 [br s, 2H (NH)]; ^{13}C NMR δ (ppm) (125 MHz, $CDCl_3$), 21.9 [CH_2, cyclohexenyl], 22.6 [CH_2, cyclohexenyl], 25.2 [(CH_2), cyclohexenyl] 25.4 [(CH_2), cyclohexenyl], 26.7 (($NCH_2CH_2)_2$), 34.2 (CO*CH*), 39.0 (($NCH_2)_2$), 50.6 ($COCH_2$), 51.6 (OCH_3), 128.1 (CH, cyclohexenyl), 132.0 (C, cyclohexenyl), 172.1 ($COOCH_3$); 172.9 (CONH). Anal. Calcd for $C_{26}H_{40}N_2O_6$ (476.61): C, 65.52; H, 8.46; N, 5.88. Found: C, 65.64; H, 8.55; N, 5.95.