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Efficient Synthesis of Isoxazolidine-Tethered Monolayer-Protected Gold Nanoparticles (MPGNs) via 1,3-Dipolar Cycloadditions under High-Pressure Conditions

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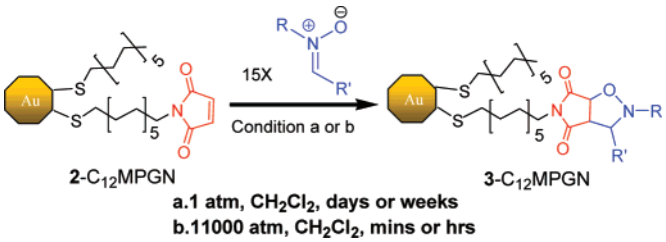

A maleimide-modified 2.5 ± 0.5 nm mixed monolayer protected gold nanoparticle (**2**-C_{12}MPGN) containing approximately 30% maleimide-terminated dodecanethiolate/dodecanethiolate ligands was prepared. The **2**-C_{12}MPGN was reacted with a series of nitrones (**a**−**i**) at both atmospheric and hyperbaric (11 000 atm) conditions to form the corresponding isoxazolidine-modified nanoparticles (**3**-C_{12}MPGN) via an interfacial 1,3-dipolar cycloaddition. At atmospheric pressures, the reaction proceeds slowly (if at all) and makes this reaction impractical for the synthetic modification of the nanoparticles. However, by performing the reaction under the high-pressure conditions, the reaction proceeds efficiently and quantitatively. TEM shows that the use of high pressure does not affect the size of the gold nanoparticle core. The **3**-C_{12}MPGNs were characterized by ^{1}H NMR spectroscopy by comparing the spectra obtained with those of model reactions utilizing *N*-dodecylmaleimide (**4**) with the same nitrones (**a**−**i**) to form **5**. Additionally, the cycloaddition reaction also occurs more readily with **4** than with **2**-C_{12}MPGN with all nitrones, indicating that the environment of the latter affects the cycloaddition reaction.

Introduction

Cycloaddition is one of the most efficient and reliable synthetic transformations for the rapid, predictable, and reliable assembly of molecular complexity. While the bulk of the attention directed toward this reaction has centered about the Diels−Alder reaction, other cycloadditions have established their place in the toolbox of the synthetic chemist. 1,3-Dipolar cycloadditions, for example, are some of the most useful ways to construct heterocyclic rings.[1] Often, simple variation of the dipolar or dipolarophilic partners offers a method for incorporation of a large degree of structural diversity. Nitrones may be the most studied of the dipolar species owing to their ability to generate the isoxazolidines with a high degree of regio- and stereochemical control. Perhaps more important than this is the access they provide to a wide variety of 1,3-aminoalcohols via reductive scission of the NO bond.

Controlling the surface chemical structure and thus the interactions between monolayer-protected gold nanoparticles (MPGNs) and solutes is a major challenge for their potential applications in device fabrications, detection systems, or drug delivery, and so developing efficient methods for preparing MPGNs remains a useful synthetic endeavor.[2] Because of the complex structures that can be introduced using cycloaddition reactions, they have been used for the synthetic modification

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(1) (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2003. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (c) Bonin, M.; Chauveau, A.; Micouin, L. *Synlett* **2006**, *15*, 2349−2363.

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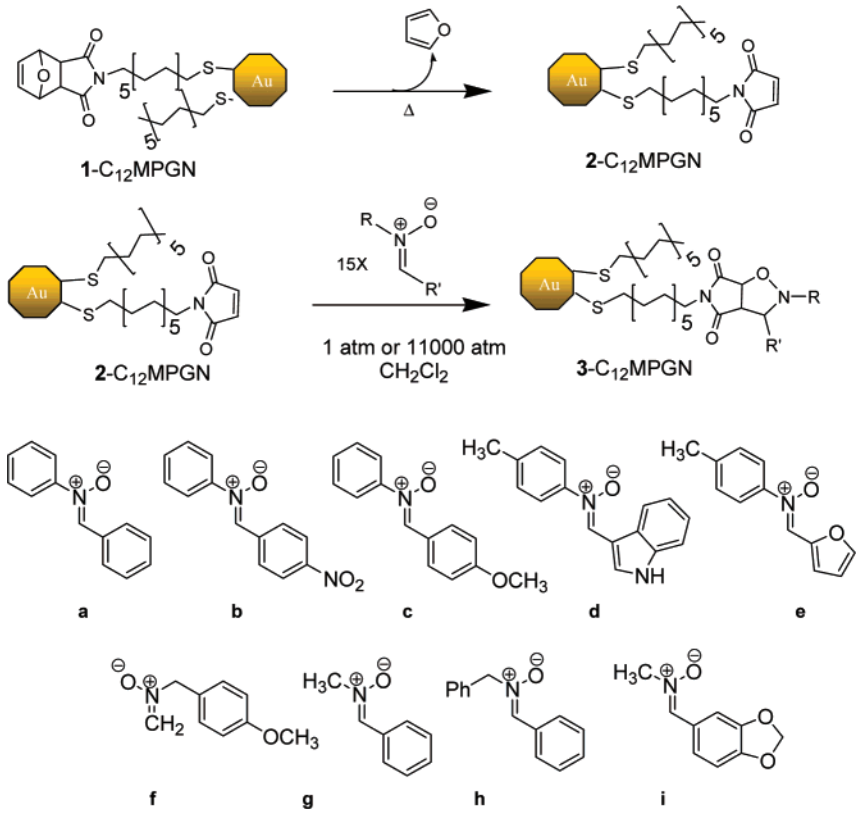
SCHEME 1. Preparation of 2-C_{12}MPGN from 1-C_{12}MPGN and the Reaction of 2-C_{12}MPGN via a 1,3-Dipolar Cycloaddition with Nitrones a−i to Form the Corresponding Isoxazolidine-Modified 3-C_{12}MPGN under Ambient and High-Pressure Conditions



of self-assembled monolayers on gold (SAMs) and MPGNs.[3,4] Due to the vast structural diversity offered by the 1,3-dipolar cycloaddition of a nitrone with an alkene and the potential to further elaborate it by reduction of the N−O bond of the product isoxazolidine, we investigated this reaction type for the synthetic modification of MPGNs.

We have previously developed a method to prepare a mixed maleimide/dodecanethiolate-modified monolayer-protected gold nanoparticle (**2**-C_{12}MPGN) and showed that it could serve as a dienophile to react via interfacial Diels−Alder reactions with a series of dienes of varying steric and electronic demand. The Diels−Alder reactions that did not proceed, or proceeded only after days, on the MPGN at ambient temperature and pressure were completed in less than 10 min at 25 °C at 11 000 atm.[4] 1,3-Dipolar cycloadditions of nitrones with alkenes, like Diels−Alder reactions, possess a negative volume activation reaction.[5] As such, they have shown to be subject to hyperbaric rate acceleration in solution. Additionally, this reaction type has been studied on polymer solid supports.[6] Kuster and Scheeren were the first to report the successful promotion of this reaction type proceeding on Wang resin solid supports under high-pressure conditions,[7] and they have continued to expand the usefulness of high-pressure-promoted cycloadditions on resin-bound reactants on solid-phase supports.[8] Prompted by these promising studies and our own success on using high pressures to promote the Diels−Alder reaction on metal nanoparticles, in this report, we examine for the first time the interfacial 1,3-dipolar nitrone/alkene cycloaddition under ambient and high pressures on MPGN. We utilized the maleimide-tethered MPGN, prepared as we described previously,[4,9] as the dipolarophile and studied the cycloaddition reaction with a series of structurally diverse nitrones to prepare isoxazolidine-modified MPGN, **3**-C_{12}MPGN (see Scheme 1). The maleimide was a useful model alkene to study this interfacial chemistry because it is a doubly activated alkene and simplifies the analysis of the products because it eliminates complications due to regioselectivity of the cycloaddition reaction because it is a symmetric alkene. The results of this study show that the slow and inefficient 1,3-dipolar

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(4) Zhu, J.; Ganton, M. D.; Kerr, M. A.; Workentin, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 4904−4905.

(5) Isaacs, N. S. In *High Pressure Techniques in Chemistry and Physics*; Holzapfel, W. W., Isaacs, N. S., Eds.; Oxford University Press: New York, 1997; Chapter 7. Unfortunately, there is no systematic activation volume data for the reactions studied herein. From the available references about 1,3-dipolar cycloadditions and Diels−Alder reactions, the activation volume for the former reaction is usually 10 cm^3/mol smaller than that of the latter.

(6) Rück-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507−516.

(7) (a) Kuster, G. J.; Scheeren, H. W. *Tetrahedron Lett.* **1998**, *39*, 3613−3616. (b) Kuster, G. J.; Scheeren, H. W. *Tetrahedron Lett.* **2000**, *41*, 515−519.

(8) See for example: (a) van Berkom, L. W. A.; Kuster, G. T. J.; Scheeren, H. W. *Mol. Diversity* **2003**, *6*, 271−282. (b) Kuster, G. J. T.; van Berkom, L. W. A.; Kalmoua, M.; van Loevezijn, A.; Sliedregt, L. A. J. M.; van Steen, B. J.; Kruse, C. G.; Rutjes, F. P. J. T.; Scheeren, H. W. *J. Comb. Chem.* **2006**, *8*, 85−94.

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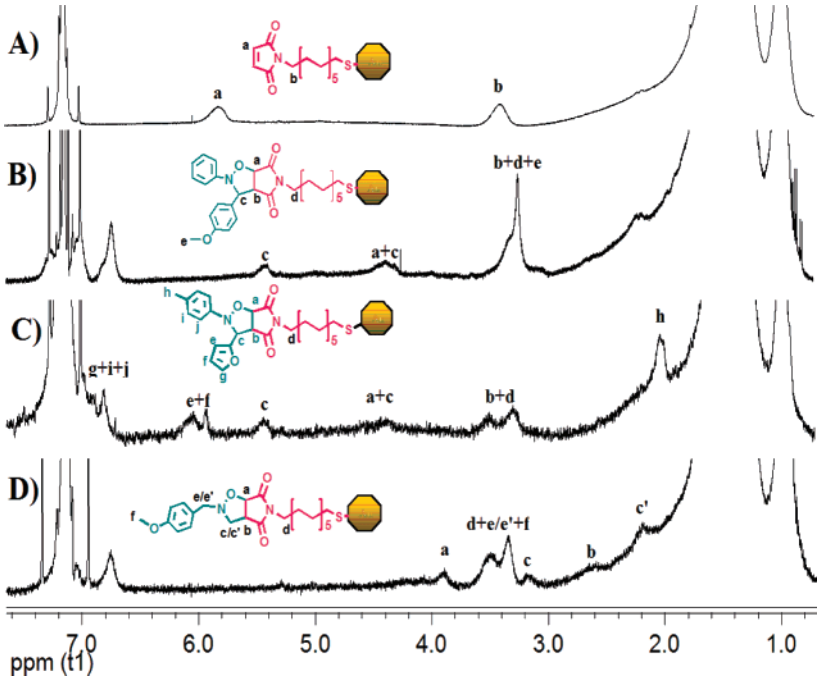


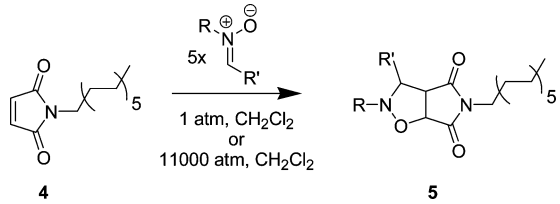
FIGURE 1. ^{1}H NMR spectra of **2**-C_{12}MPGN (A) and representative **3**-C_{12}MPGN formed in 1,3-dipolar cycloaddition of **2**-C_{12}MPGN with nitrones **c**, **e**, and **f**: (B) **3c**-C_{12}MPGN; (C) **3e**-C_{12}MPGN; (D) **3f**-C_{12}MPGN. Solvent C_6D_6.

cycloaddition reactions of **2**-C_{12}MPGNs with various nitrones under ambient pressure are greatly accelerated under hyperbaric conditions, making it a synthetically viable reaction for the modification of these nanoparticles.

Results and Discussion

The dipolarophile MPGN, **2**-C_{12}MPGN, was prepared using the method reported before.[4,9] Dodecanethiolate-modified nanoparticles (C_{12}-MPGN) were prepared following the Brust−Schiffrin method using a 1:1 ratio of dodecanethiol/hydrogen tetrachloroaurate with TOAB and a 10-fold excess of $NaBH_4$.[10] The Diels−Alder-protected furan maleimide dodecyl thiol (**1**) was then incorporated onto the C_{12}-MPGN using C_{12}-MPGN/**1** in a 1:1.5 ratio by the standard place-exchange method,[11] and then the maleimide-containing MPGN (**2**-C_{12}MPGN) is liberated by heating the **1**-C_{12}MPGN in toluene to initiate the release of furan off of the MPGN and into solution. Compound **2**-C_{12}-MPGN (Scheme 1) with an average core size of 2.5 ± 0.5 nm is then isolated pure after removal of the liberated furan by washing with 95% ethanol. The ^{1}H NMR spectrum of **2**-C_{12}-MPGN dissolved in C_6D_6 exhibits the characteristic broad NMR signals observed for substrates immobilized on a MPGN; however, importantly, the chemical shifts (and integration) allow for the structural characterization of the functionality on the MPGN (Figure 1A). Diagnostic in the spectrum of **2**-C_{12}MPGN are the olefinic protons arising from the maleimide moiety at 5.80 ppm (labeled a) and the methylene protons α to the N at 3.40 ppm (labeled b). The broad signals from ca. 1.1−2.0 ppm are due to CH_2 resonances in the alkyl chains of the ligands, and the terminal CH_3 group of the C_{12} ligand appears as the smaller broad signal at 0.9 ppm. The MPGN contains ca. 30% maleimide compared to C_{12}.[4,9]

SCHEME 2. Model Reaction of 4 with Nitrones to Form Isoxazolidine Product 5



To probe the synthetic utility of the nitrone cycloaddition, **2**-C_{12}MPGN was mixed with a 15 times molar excess of each of the nitrones dissolved in CH_2Cl_2 as the solvent. Half of each solution was purged with argon and left at ambient conditions (1 atm, 25 °C), and the other half was placed in a Teflon tube, argon-purged, sealed, and placed in a high-pressure reactor and subjected to pressures of 11 000 atm at room temperature (Scheme 1). Because of the breadth of the NMR signals of the substrates on a MPGN, it was important to gain information as to what chemical shifts to expect for the isoxazolidine products formed on reaction of each nitrone with **2**-C_{12}MPGN. Therefore, model reactions were also carried out. Namely, each nitrone (**a**−**i**) was mixed with *N*-dodecylmaleimide (**4**) in a 5:1 ratio in CD_2Cl_2, argon-purged, and subjected to atmospheric and high-pressure conditions (Scheme 2). The progress of the 1,3-dipolar cycloaddition reactions was monitored by ^{1}H NMR spectroscopy following the disappearance of the olefinic protons of the maleimide moiety on **2**-C_{12}MPGN (and **4**) and by the concomitant appearance of signals that could be assigned to the corresponding isoxazolidine cycloadducts (**3**-C_{12}MPGN and **5**, respectively).

Figure 1B−D shows representative NMR spectra of the **3**-C_{12}-MPGN obtained from the reaction of **2**-C_{12}MPGN with nitrones **c**, **e**, and **f**, respectively, after completion of the reaction and

(10) Brust, M.; Walker, M.; Bethell, D.; Schiffrin, D. J.; Whyman, R. J. *Chem. Commun.* **1994**, 801−802.

(11) (a) Hostetler, M. J.; Templeton, A. C.; Murray, R. W. *Langmuir* **1999**, *15*, 3782−3789. (b) Brust, M.; Kiely, C. J. *Colloids Surf. A* **2002**, *202*, 175−186.

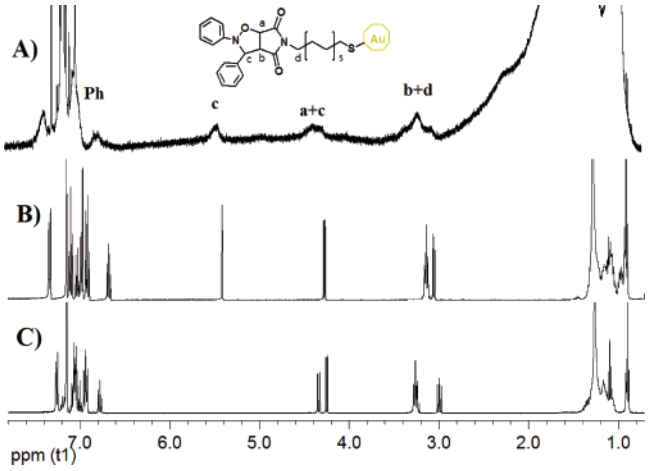


FIGURE 2. Representative ^{1}H NMR spectra of the products from 1,3-dipolar cycloaddition reaction of (A) **2**-C_{12}MPGN with nitrone **a** to yield **3a**-C_{12}MPGN as a mixture of the diastereomers and **4** with nitrone **a** to yield (B) **5a**-exo and (C) **5a**-endo, respectively. Solvent C_6D_6.

removal of the excess nitrone. The broad signals assigned to the various isoxazolidine protons on the **3**-C_{12}MPGN are indicated in the figure and were confirmed by assigning the spectra of **5** obtained in the model reactions. Full characterization, including NMR spectral assignments of the products for the model reactions and comparisons to those on the MPGN, is provided in the Experimental Section and Supporting Information for all the reactions. Of course, there are two diastereomers, the *exo* and *endo* products, expected to be formed in these cycloadditions. For the model 1,3-dipolar cycloaddition reactions, these diastereomers were separated by preparative TLC and characterized; their structures were determined with the aid of 1-D NOESY experiments. By knowing the chemical shifts of the relevant protons of the *exo* and *endo* diastereomers, we were able to examine the reactions on **3**-C_{12}MPGN. A representative example showing the comparison of the products from the model reaction (**4** → **5**) to that on the particle (**2**-C_{12}MPGN → **3**-C_{12}MPGN) is shown in Figure 2 for the reaction of **2**-C_{12}MPGN (and **4**) with nitrone **a** to form **3a**-C_{12}MPGN (or **5a** *exo* and *endo*). Similar figures for reactions of **2**-C_{12}MPGN with the other nitrones are in the Supporting Information. The *exo*/*endo* ratio of the products from reaction of **4** under the ambient and high-pressure conditions was able to be determined as 5:3 from ^{1}H NMR integration of the product mixture. Because of the inherent breadth of the signals of the isoxazolidine ligands on **3**-C_{12}MPGN, the *exo*/*endo* ratio could not be as easily determined, although it is clear that both isomers are formed (see Figure 2). Because there is no obvious bias in the broad signal in the NMR spectrum toward any one diastereomer that is not expected from the result with the model compound, the results suggest that under high-pressure conditions the reactions on the MPGN do not show a significant difference in diastereoselectivity. There is no noticeable change in the *exo*/*endo* ratio in **3**-C_{12}MPGN, and it appears that they are formed in roughly the same ratio as in the model reaction.[12] In several cases, the **3**-C_{12}MPGN was reduced using iodine reduction with the result that the ligands come off as disulfides. Because the disulfides are now in solution, the proton NMR signals for the isoxazolidines can be resolved. The ratio of *exo*/*endo* cleaved off the **3**-C_{12}MPGN was the same as the ratio determined for the model reaction (**4** → **5**, i.e., 5:3; see the Supporting Information for an example).

TABLE 1. Times for Quantitative Formation of Isoxazolidines (3a−i-C_{12}MPGN and 5a−i) from the 1,3-Cycloaddition Reactions between 2-C_{12}MPGN or 4 with Nitrones a−i under Ambient Atmospheric Pressures (1 atm, 25 °C) and Hyperbaric Pressures (11 000 atm, 25 °C)[a]

	4		**2**-C_{12}MPGN	
product	1 atm, 25 °C	11000 atm	1 atm	11000 atm
3a, **5a**	10 h	10 min	1 day	10 min
3b, **5b**	30 h	10 min	3 days	10 min
3c, **5c**	20 h	10 min	2 days	10 min
3d, **5d**[b]	50% in 14 days	10 min	>2 weeks[c]	30 min
3e, **5e**	3 days	10 min	7 days	10 min
3f, **5f**	2 h	10 min	2 h	10 min
3g, **5g**	7 days	10 min	17 days	10 min
3h, **5h**	12 days	30 min	>2 weeks[c]	60 min
3i, **5i**	14 days	30 min	>2 weeks[c]	60 min

[a] Times indicate to reaction completion (or as indicated) as determined by ^{1}H NMR spectroscopy. [b] Due to the poor solubility of **d** in CD_2Cl_2, the ratio of **4**/**d** is 1:1.5. [c] Less than 50% conversion after 14 days.

For each reaction, the time taken to convert completely the maleimide moiety to the isoxazolidine was determined by following the reaction by ^{1}H NMR spectroscopy and monitoring the complete loss of the signals due to the maleimide olefinic protons. The results indicating these times are summarized in Table 1. Table 1 shows that under hyperbaric conditions the 1,3-dipolar cycloaddition reactions are quantitative and occur in reaction times that are remarkably shorter than those under ambient pressure (compare results for conditions **a** and **b** for **2**-C_{12}MPGN). Reactions that take days or even weeks are all complete in less than 60 min at 11 000 atm and most in 10 min or less. The minimum reaction time in the high-pressure reactor is 10 min because this is the time it takes to pressurize and depressurize the reaction vessel. Comparing reaction conditions at 1 atm for the reactions of **4** and **2**-C_{12}MPGN, it is not surprising that all the nitrones (**a**−**i**) react more readily with **4**, even with a lower concentration of nitrone. This is likely because the MPGN offers a unique environment providing steric effects to the reaction.

Although the reactions summarized were all performed on a small scale (because of the cost of the MPGN), the reactions are scalable. For example, similar reactions carried out at the 50 mg scale proceed rapidly and quantitatively at high pressure (see Supporting Information for details). In fact, the reactor used will allow these reactions on the several gram scale, making the use of hyperbaric reactions on MPGN practical for applications and further synthetic elaborations.

Examining Table 1 more carefully, there are differences in the reactivity of various nitrones with both **4** and **2**-C_{12}MPGN under ambient pressures, and this is presumably determined by the different electronic and steric demands of the substituents R and R′ on the nitrone. The inductive effect of a *N*-aryl substitute group (R) increases the dipolar nature of the nitrone (**a**, **b**, **c**, and **e**), and as a result, *N*-aryl nitrones generally reacted faster than the *N*-alkyl-substituted nitrones (**g**−**i**). For nitrone **d**, its larger steric demand resulted in the much lower apparent reactivity compared to that of other *N*-aryl nitrones. The difference in reactivity between nitrones **g** and **h** can likely be explained through the smaller steric effect of N−CH_3 in **g**

(12) The issues of *exo*/*endo* selectivity in 1,3-dipolar cycloadditions is still a matter of discussion, and we make no attempt to rationalize the ratio. For examples of reactions of N-substituted maleimides with nitrones, see: (a) Cokun, N.; Mert, H.; Arikan, N. *Tetrahedron* **2006**, *62*, 1351−1359. (b) Cokun, N.; Öztürk, A. *Tetrahedron* **2007**, *63*, 1402−1410.

compared to that of the *N*-benzyl in **h**. Nitrone **f** has small steric demands on the carbon terminus of the nitrone, making it the most efficient nitrone under ambient pressure. The stronger electron-donating substituents on nitrone **i** compared to **g** affects the dipole and nearly doubles the reaction time for the former. It is also worth pointing out that, for nitrone **e**, even though it contains both a nitrone group and a furan diene, no Diels−Alder adducts of furan with the maleimide were detected from this reaction. This may be attributed to a more negative activation volume expected for the 1,3-cycloaddition than for the Diels−Alder reaction.

In general, the 1,3-dipolar cycloaddition reactions of various nitrones with **4** or **2**-C_{12}MPGNs take from hours to weeks at ambient conditions. After applying a high pressure of 11 000 atm, all these reactions are greatly accelerated and complete within 1 h, and for most cases, within 10 min. Importantly, TEM analysis of particles before and after exposure to hyperbaric conditions shows that, even after applying 11 000 atm on **2**-C_{12}-MPGNs for 24 h, their core size is not affected (Supporting Information). Thus the only effect of the high pressure is a significant acceleration of the cycloaddition.

Conclusions

We demonstrate for the first time that by using hyperbaric conditions we are able to introduce complex isoxazolidine functionality at the interface of a nanoparticle via 1,3-dipolar cycloaddition of a nitrone with an alkene. Such synthetic transformations at ambient conditions on these particles are impractical because they are so slow and proceed to poor conversions. Of particular note is that the use of high-pressure reaction conditions does not alter the integrity of the metal core of the MPGN. Although the maleimide-tethered MPGN was used as the dipolarophile for this proof of concept, in practice, any suitably activated alkene-tethered MPGN and indeed nitrone-modified MPGN could be used as the reaction template for the preparation of isoxazolidine-modified MPGNs which can be further elaborated synthetically by cleavage of the N−O bond to yield gold-supported aminoalcohol moieties which in turn could be further derivatized. This aspect to incorporate synthetic diversity for the modification of MPGNs is currently under investigation. Besides being a useful approach to accelerate cycloaddition reactions in solution, our work illustrates that hyperbaric chemistry is a useful tool to be exploited generally for the efficient and rapid synthetic surface modification of MPGNs (and perhaps other nanoparticles) using reactions that are subject to such acceleration.

Experimental Section

General. The compounds dodecanethiol, hydrogen tetrachloroaurate(III), tetraoctylammoniun bromide, 1,12-dibromododecane, benzene-d_6, chloroform ($CDCl_3$), and dichloromethane (CD_2Cl_2) were used as received from suppliers. The high-pressure reactions were carried out on a commercially available reactor at 11 000 atm at room temperature. Proton NMR and ^{13}C NMR spectra were recorded on either a 600 or a 400 MHz spectrometer (as noted) in deuterated chloroform, deuterated methylene chloride, or deuterated benzene solutions and are reported in parts per million (ppm), with the solvent resonance used as a reference. Compound **2**-C_{12}MPGN was prepared using a protocol we previously reported.[4,9] The nitrones **a**−**i** used in this study were prepared following reported procedures.[13] Other general information can be found in the Supporting Information.

General Procedure for the 1,3-Dipolar Cycloaddition Reactions of 2-C_{12}MPGN with Nitrones a−i at High Pressure and Ambient Conditions. Typically, 10 mg of **2**-C_{12}MPGN was dissolved in 2.0 mL of CD_2Cl_2 then mixed with 15 equiv of the nitrones (**a**−**i**). The mixture was then separated into two parts. One portion was transferred into a brass-clamp sealed PTFE tube under argon and placed in the high-pressure reactor at 11 000 atm. The other portion was purged with argon and left to react under ambient conditions (1 atm, 25 °C) for comparison. The products, **3(a**−**i)**-C_{12}MPGN, were purified by washing with 95% ethanol and CH_3-CN to remove excess nitrone. ^1H NMR spectroscopy was used to check the completion and purity of **3(a**−**i)**-C_{12}MPGNs. The disappearance of the peak at 5.80 ppm, which was due to the olefinic protons of the maleimide moiety, was used to determine the completion of these reactions. In a few cases, the reactions were also performed at higher concentrations (50 mg) of **2**-C_{12}MPGN.

General Procedure for the 1,3-Dipolar Cycloaddition Reactions of *N*-Dodecylmaleimide (4) with Nitrones a−i at High Pressure and Ambient Conditions. Typically, 10 mg of *N*-dodecylmaleimide and 5 equiv of the nitrone (**a**−**i)**, except for nitrone **d**, were dissolved in 2.0 mL of CD_2Cl_2. Due to the poor solubility of nitrone **d** in CD_2Cl_2, the ratio of *N*-dodecylmaleimide/**d** used was 1:1.5. The mixture was separated into two portions. One portion was purged with argon in a NMR tube and left to react under ambient conditions (1 atm, 25 °C). The other portion was transferred into a brass-clamp sealed PTFE tube under argon and placed in the high-pressure reactor at 11 000 atm. The reactions were monitored by ^1H NMR spectroscopy. The product was then separated by preparative TLC and characterized. Two diastereomers were generated, and their conformations were confirmed by 1-D NOESY. The *exo*/*endo* ratio was determined as 5:3 from the crude ^1H NMR spectra.

***N*-Dodecylmaleimide (4).** Maleimide (4.00 g, 41.2 mmol) and furan (4.20 g, 62.0 mmol) were dissolved in 30 mL of diethyl ether in a sealed tube and heated to 90−100 °C for 12 h. The 3,6-endoxo-Δ^4-tetrahydrophthalhide (furan-masked maleimide) precipitated as a white solid after cooling the mixture to room temperature. The product was then filtered and washed with 3 × 10 mL of cold diethyl ether to remove the unreacted maleimide, giving rise to a yield of 6.0 g (89%). The NMR spectrum of 3,6-endoxo-Δ^4-tetrahydrophthalhide indicates that the product is exclusively the *exo* isomer: ^1H NMR ($CDCl_3$, 600 MHz) δ 8.10 (br s, ^1H), 6.52 (d, J = 0.782 Hz, 2H), 5.31 (d, J = 0.782 Hz, 2H), 2.89 (s, 2H); ^{13}C NMR ($CDCl_3$, 600 MHz) δ 175.9, 136.5, 80.9, 48.7; IR (dropcast on NaCl plate, cm^{-1}) ν 3185, 3089, 3029, 2995, 1705, 1356, 1258, 1189, 856, 822. MS (EI); *m*/*z* (%) 165.1(4.9), 138-(3.6), 121(2), 68(100); exact mass ($C_8H_7O_3N$) calcd 165.0426, found 165.0422. The 3,6-endoxo-Δ^4-tetrahydrophthalhide (6.0 g, 36.6 mmol) and 1-dibromododecane (26.6 mL, 146.4 mmol) were dissolved in 70 mL of dry DMF. K_2CO_3 (6.0 g, 43.9 mmol) was added, and the mixture was heated to 50 °C for 3 h. The mixture was then dissolved in 200 mL of diethyl ether and washed with 5% HCl, followed by water to remove DMF. The organic layer was then dried with magnesium sulfate and evaporated to dryness. The crude product was purified by liquid column chromatography (10% EtOAc/hexane) to isolate the furan-protected dodecylmaleimide (10.25 g, white crystal, 84% yield). This product was then heated at reflux in 200 mL of toluene overnight to effect a retro-Diels−Alder reaction. After removal of toluene, the crude product was subjected to column chromatography (10% EtOAc/hexane) to yield 6.69 g (81% yield) of *N*-dodecylmaleimide as a white crystalline solid: mp 57.7−58.2 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.67 (s, 2H), 3.50 (t, J = 7.27 Hz, 2H), 1.56 (quintet, 2H), 1.1−1.3 (br, 18H, a quintet at 1.26 ppm was merged with the broad

(13) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554−8557 and reference therein.

peak), 0.87 (t, J = 6.70 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8 (2C), 134.0 (2C), 37.9, 31.8, 29.6 (2C), 29.5, 29.4, 29.3, 29.1, 28.5, 26.7, 22.7, 14.1; IR (dropcast on NaCl, cm^{-1}) ν 3078, 2919, 2816, 1698, 1465, 1446, 1403, 1371, 1124, 692; MS (EI) exact mass ($C_{16}H_{27}O_2N$) calcd 265.2042, found 265.2046.

Isoxazolidine 5a-exo: ^{1}H NMR (C_6D_6, 400 MHz) δ 7.35 (m, 2H), 7.10 (m, 2H), 7.05−6.97 (m, 3H), 6.92 (m, 2H), 6.68 (m, 1H), 5.42 (s, 1H), 4.29 (d, J = 7.4 Hz, 1H), 3.14 (t, J = 7.3 Hz, 2H), 3.06 (d, J = 7.4 Hz, 1H), 1.28−1.08 (br, 18H), 0.95−0.91 (m, 3H, a quintet merge together with a triplet, J = 7.0 Hz); ^{13}C NMR (C_6D_6, 400 MHz) δ 174.5, 172.9, 148.8, 139.3, 128.9 (2C), 128.7 (2C), 126.8 (3C), 122.4, 114.6 (2C), 77.1, 69.8, 57.2, 39.1, 32.1, 29.8 (2C), 29.7, 29.5, 29.6, 29.3, 26.7, 26.8, 22.9, 14.1; FT-IR (dropcast on NaCl, cm^{-1}) ν 3069, 3036, 2924, 1734, 1480, 1457, 1163, 1024, 715; HRMS calcd m/z for $C_{29}H_{38}N_2O_3$ 462.2882, found 462.2895.

Isoxazolidine 5a-endo: ^{1}H NMR (C_6D_6, 400 MHz) δ 7.27 (m, 2H), 7.10−7.00 (m, 5H), 6.94 (m, 2H), 6.79 (m, 1H), 4.36 (d, J = 9.1 Hz, 1H), 4.27 (d, J = 7.8 Hz, 1H), 3.27 (t, J = 7.9 Hz, 2H), 3.0 (dd, J = 7.8, 9.1 Hz, 1H), 1.28−1.08 (br, 18H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (C_6D_6, 400 MHz) δ 173.4, 171.3, 148.0, 135.2, 128.6 (2C), 128.5 (2C), 128.3, 124.2 (2C), 121.8, 118.8 (2C), 76.8, 70.9, 54.4, 38.8, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.2, 27.7, 26.9, 22.9. 14.1; FT-IR (dropcast on NaCl, cm^{-1}) ν 3070, 3050, 2926, 1713, 1479, 1265, 1031, 740; HRMS calcd m/z for $C_{29}H_{38}N_2O_3$ 462.2882, found 462.2878.

3a-C$_{12}$MPGN: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.38, 7.15−7.02 (merge with solvent), 6.78, 5.45, 4.37, 4.28, 3.19, 1.39, 0.98.

Isoxazolidine 5b-exo: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.80 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.9 (m, 4H), 6.70 (m, 1H), 5.23 (s, 1H), 4.16 (d, J = 7.5 Hz, 1H), 3.15 (t, J = 7.5 Hz, 2H), 2.75 (d, J = 7.5 Hz, 1H), 1.29−1.20 (br, 20H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C NMR (600 MHz, C_6D_6) δ 174.0, 172.7, 148.4, 147.8, 145.5, 129.3 (2C), 127.5 (2C), 123.9 (2C), 123.2, 114.8 (2C), 77.1, 69.1, 56.9, 39.4, 32.3, 30.1, 30.0 (2C), 29.8, 29.7, 29.5, 27.1, 27.0, 23.1, 14.4; FT-IR (dropcast on NaCl, cm^{-1}) ν 2917, 2850, 1709, 1517, 1488, 1468, 1353, 1224, 1198, 1141, 1024, 838, 767, 751, 719, 700, 689, 614; HRMS calcd m/z for $C_{29}H_{37}N_3O_5$ 507.2733, found 507.2729.

Isoxazolidine 5b-endo: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.79 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 6.99 (t, J = 7.8 Hz, 2H), 6.91 (dd, J = 8.6, 7.8 Hz, 2H), 6.83 (t, J = 7.8 Hz, 1H), 4.22 (m, 2H), 3.20 (t, J = 7.4 Hz, 2H), 2.89 (dd, J = 7.8, 9.0 Hz, 1H), 1.30−1.20 (br, 18H), 1.02 (quintet, 2H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (400 MHz, C_6D_6) δ 173.0, 171.2, 148.1, 147.3, 141.9, 129.1 (2C), 128.6 (2C), 125.1, 123.8 (2C), 119.1 (2C), 77.0, 69.9, 54.4, 39.1, 32.3, 30.1 (2C), 30.0, 29.9, 29.8, 29.4, 27.9, 27.0, 23.1, 14.3; FT-IR (dropcast on NaCl, cm^{-1}) ν 2919, 2851, 1710, 1594, 1522, 1489, 1466, 1454, 1350, 1259, 1094, 1071, 868, 853, 767, 752, 722, 693; HRMS calcd m/z for $C_{29}H_{37}N_3O_5$ 507.2733, found 507.2729.

3b-C$_{12}$MPGN: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.84, 7.05−7.02 (merge with solvent), 6.79, 5.28, 4.25, 3.32, 3.22, 1.38, 0.97.

Isoxazolidine 5c-exo: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.24 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 6.94 (t, J = 7.3 Hz, 2H), 6.73 (d, J = 8.6 Hz, 2H), 6.69 (t, J = 7.3 Hz, 1H), 5.39 (s, 1H), 4.32 (d, J = 7.4 Hz, 1H), 3.24 (s, 3H), 3.20 (t, J = 7.3 Hz, 2H), 3.08 (d, J = 7.4 Hz, 1H), 1.29−1.02 (br, 18H), 1.02 (quintet, 2H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (600 MHz, C_6D_6) δ 174.8, 173.2, 159.7, 148.9, 131.2, 129.1 (2C), 128.4 (2C), 122.6, 115.2 (2C), 114.4 (2C), 77.2, 69.8, 57.5, 54.8, 39.3, 32.3, 30.10, 30.08, 29.99, 29.86, 29.00, 29.5, 27.2, 27.0, 23.1, 14.4; FT-IR (dropcast on NaCl, cm^{-1}) ν 2925, 2854, 1710, 1597, 1514, 1492, 1463, 1400, 1371, 1347, 1305, 1251, 1160, 1033, 832, 803, 755, 693, 621; HRMS calcd m/z for $C_{30}H_{40}N_2O_4$ 492.2988, found 492.3002.

Isoxazolidine 5c-endo: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.21 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 6.98 (t, J = 7.4 Hz, 2H), 6.80 (t, J = 7.4 Hz, 1H), 6.71 (d, J = 8.7 Hz, 2H), 4.38 (d, J = 9.0 Hz, 1H), 4.29 (d, J = 7.8 Hz, 1H), 3.32 (m, 2H), 3.20 (s, 3H), 3.02 (dd, J = 9.0, 7.8 Hz, 1H), 1.28−1.10 (br, 20H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (400 MHz, C_6D_6) δ 173.8, 171.8, 160.1, 148.5, 129.2 (2C), 128.9 (2C), 127.1, 124.4, 119.1 (2C), 114.4 (2C), 77.0, 70.9, 54.68, 54.59, 39.0, 32.3, 30.08 (2C), 30.03, 29.89, 29.80, 29.52, 28.0, 27.2, 23.1, 14.4; FT-IR (dropcast on NaCl, cm^{-1}) ν 2921, 2852, 1711, 1613, 1598, 1513, 1491, 1467, 1453, 1401, 1250, 1173, 1072, 1033, 821, 759, 692; HRMS calcd m/z for $C_{30}H_{40}N_2O_4$ 492.2988, found 492.2996.

3c-C$_{12}$MPGN: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.28, 7.10 (merge with solvent), 7.02, 6.74, 5.42, 4.38, 3.25, 1.38, 0.97.

Isoxazolidine 5d-exo: ^{1}H NMR (C_6D_6, 400 MHz) δ 8.03 (m, 1H), 7.24−7.22 (m, 2H), 7.04−7.02 (m, 3H), 6.90 (m, 1H), 6.81 (s, 1H), 6.76 (d, J = 8.18 Hz, 2H), 5.84 (s, 1H), 4.39 (d, J = 7.5 Hz, 1H), 3.37 (d, J = 7.5 Hz, 1H), 3.18 (t, J = 7.9 Hz, 3H), 1.98 (s, 3H), 1.29−0.98 (br, 20H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (C_6D_6, 400 MHz) δ 175.1, 173.8, 147.2, 136.9, 131.7, 129.8 (2C), 125.9, 122.7 (2C), 120.5, 119.1, 115.2 (2C), 114.1, 111.7, 77.6, 64.8, 56.4, 39.2, 32.3, 30.1 (2C), 30.0, 29.9, 29.8, 29.6, 27.1, 27.0, 23.1, 20.5, 14.4; FT-IR (dropcast on NaCl, cm^{-1}) ν 3440 (br), 3091, 3072, 3036, 2925, 2854, 1960, 1713, 1616, 1507, 1465, 1248, 1036, 1018, 821, 749, 676; HRMS calcd m/z for $C_{32}H_{41}N_3O_3$ 515.3148, found 515.3163.

Isoxazolidine 5d-endo: ^{1}H NMR (C_6D_6, 400 MHz) δ 7.79 (m, 1H), 7.23−7.17 (merged in the C_6D_6 solvent peak, 2H), 7.13 (m, 1H), 6.98 (m, 1H), 6.91 (s, 1H), 6.73−6.71 (m, 3H), 4.83 (d, J = 8.6 Hz, 1H), 4.40 (d, J = 7.8 Hz, 1H), 3.37−3.28 (m, 2H), 3.15 (t, J = 8.6, 7.8 Hz, 1H), 1.91 (s, 3H), 1.29−1.08 (br, 20H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (C_6D_6, 400 MHz) δ 174.2, 171.9, 145.9, 136.3, 133.9, 129.2 (2C), 126.4, 123.3, 122.4, 120.0 (2C), 119.8, 119.5, 111.4, 109.5, 76.8, 65.7, 53.8, 38.8, 32.1, 29.9 (2C), 29.8, 29.7, 29.6, 29.3, 27.6, 26.9, 22.9, 20.4, 14.1; FT-IR (dropcast on NaCl, cm^{-1}) ν 3442, 3104, 2954, 2918, 2850, 1706, 1617, 1457, 1374, 1265, 1023, 1019, 742; HRMS calcd m/z for $C_{32}H_{41}N_3O_3$ 515.3148, found 515.3157.

3d-C$_{12}$MPGN: ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 7.38, 6.99, 6.87, 6.31, 6.24, 5.03, 3.95, 3.81, 3.46, 3.27, 2.24, 1.26, 0.88.

Isoxazolidine 5e-exo: ^{1}H NMR (C_6D_6, 400 MHz) δ 6.99 (s, 1H), 6.88 (d, J = 8.1 Hz, 2H), 6.74 (d, J = 8.1 Hz, 2H), 6.01 (s, 1H), 5.93 (s, 1H), 5.40 (s, 1H), 4.45 (d, J = 7.4 Hz, 1H), 3.34 (d, J = 7.4 Hz, 1H), 3.21 (t, J = 7.4 Hz, 2H), 1.96 (s, 3H), 1.26−1.08 (br, 18H), 0.90 (t, J = 6.7 Hz, 3H); ^{13}C NMR (C_6D_6, 400 MHz) δ 174.5, 173.4, 151.2, 145.6, 142.6, 132.3, 129.6(2C), 115.9(2C), 110.7, 108.7, 76.8, 64.4, 53.9, 39.2, 32.3, 30.1 (2C), 30.0, 29.9, 29.8, 29.5, 27.3, 27.0, 23.1, 20.5, 14.4; FT-IR (dropcast on NaCl, cm^{-1}) ν 2924.41,2854.04, 1713.59, 1616.98, 1507.08, 1465.21, 1399.94, 1345.94, 1149.64, 1016.79, 741.33; HRMS calcd m/z for $C_{28}H_{38}N_2O_4$ 466.2832, found 466.2839.

Isoxazolidine 5e-endo: ^{1}H NMR (C_6D_6, 400 MHz) δ 7.08 (dd, J = 1.8, 0.8 Hz, 1H), 6.99 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.08 (d, J = 3.25 Hz, 1H), 5.97 (dd, J = 3.25, 1.8 Hz, 1H), 4.34 (d, J = 8.6 Hz, 1H), 4.22 (d, J = 7.6 Hz, 1H), 3.45 (t, J = 7.4 Hz, 2H), 2.99 (dd, J = 8.6, 7.6 Hz, 1H), 1.96 (s, 3H), 1.56 (quintet, 2H), 1.27−1.23 (br, 18H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (C_6D_6, 400 MHz) δ 143.0, 134.0, 129.5 (2C), 119.9 (2C), 110.8, 110.3, 76.6, 66.7, 52.8, 39.2, 32.3, 30.1, 30.07, 30.03, 29.97, 29.81, 29.58, 28.0, 27.1, 23.1, 20.7, 14.4. Two carbonyl carbon signal were not observed. However, the presence of the carbonyl group was verified by the strong carbonyl absorption peaks from FT-IR spectra: FT-IR (dropcast on NaCl, cm^{-1}) ν 2917, 2903, 2849, 1918, 1844, 1700, 1506, 1457, 1275, 1267, 1261, 1124, 764, 749, 668; HRMS calcd m/z for $C_{28}H_{38}N_2O_4$ 466.2832, found 466.2825.

3e-C$_{12}$MPGN: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.02 (merge with solvent), 6.91, 6.82, 6.05, 5.93, 5.43, 4.36, 3.48, 3.30, 1.38, 0.98.

Isoxazolidine 5f: ^{1}H NMR (C_6D_6, 400 MHz) δ 7.0 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 4.05 (d, J = 7.3 Hz, 1H), 3.91 (d, J = 13.2 Hz, 1H), 3.49 (d, J = 13.2 Hz, 1H), 3.42 (t, J = 7.2 Hz, 2H), 3.26 (s, 3H), 3.16 (d, J = 8.6 Hz, 1H), 2.57 (t, J = 7.3 Hz, 1H), 2.06 (br, 1H), 1.585 (quintet, 2H), 1.26−1.20 (br, 18H),

0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, C_6D_6) δ 175.8, 159.7, 130.2 (2C), 128.1, 127.9, 114.1 (2C), 75.9, 60.5, 57.7, 54.7, 48.4, 38.9, 32.3, 30.10, 30.08, 30.06, 29.96, 29.80, 29.55, 27.93, 26.99, 23.1, 14.3; FT-IR (dropcast on NaCl, cm^{-1}) ν 2925, 2854, 1785, 1709, 1685, 1613, 1514, 1465, 1457, 1438, 1400, 1368, 1349.33, 1303, 1248, 1174, 1036, 860, 822, 803, 668, 627; HRMS calcd *m*/*z* for $C_{25}H_{38}N_2O_4$ 430.2832, found 430.2836.

3f-C$_{12}$MPGN: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.06 (merge with solvent), 6.76, 3.90, 3.50, 3.36, 3.16, 2.60, 2.17, 1.39, 0.97.

Isoxazolidine 5g-exo: ^{1}H NMR was collected at 70 °C (600 MHz, C_6D_6) δ 7.12−7.10 (m, 4H), 7.08 (m, 1H), 4.34 (d, J = 7.3 Hz, 1H), 3.95 (br, 1H), 3.46 (t, J = 7.3 Hz, 2H), 3.03 (dd, J = 7.3, 3.3 Hz, 1H), 2.26 (s, 3H), 1.61 (quintet, 2H), 1.28−1.25 (br, 18H), 0.89 (t, J = 7.0 Hz, 3H). ^{1}H NMR in C_6D_6 was also provided here for comparison. One key proton was missing and the other peaks were generally broad: ^{1}H NMR (600 MHz, C_6D_6) δ 7.10−7.08 (br, 4H), 4.27 (br, 1H), 3.46 (br, 2H), 2.95 (dd, J = 7.3, 3.6 Hz, 1H), 2.20 (br, 3H), 1.6 (br, 2H), 1.27−1.22 (br, 18H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (400 MHz, C_6D_6) δ 175.2, 175.1, 128.8, 128.5 (2C), 128.1, 127.9, 76.3 (2C), 57.5 (br), 39.0, 32.3, 30.08 (2C), 29.99, 29.92, 29.8, 29.5, 27.9, 27.0, 23.1, 14.3, one carbon of the isoxazoline was too weak to be observed; FT-IR (dropcast on NaCl, cm^{-1}) ν 3091, 3072, 3037, 2953, 2854, 1717, 1465, 1036, 674; HRMS calcd *m*/*z* for $C_{24}H_{36}N_2O_3$ 400.2725, found 400.2714.

Isoxazolidine 5g-endo: ^{1}H NMR (C_6D_6, 400 MHz) δ 7.13 (merged in the solvent peak, 2H), 7.09 (m, 3H), 4.10 (d, J = 7.4 Hz, 1H), 3.38 (t, J = 7.3 Hz, 2H), 3.24 (d, J = 8.6 Hz, 1H), 2.83 (dd, J = 8.6, 7.4 Hz, 1H), 2.34 (s, 3H), 1.55 (m, 2H), 1.27−1.21 (br, 18H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (400 MHz, C_6D_6) δ 174.6, 172.3, 134.6, 128.7 (2C), 128.1 (2C), 127.9, 76.4, 75.5, 54.4, 42.4, 39.0, 32.3, 30.1, 30.0 (2C), 29.9, 29.7, 29.5, 28.2, 27.2, 23.1, 14.3; FT-IR (dropcast on NaCl, cm^{-1}) ν 3091, 3071, 3058, 2953, 2850, 1714, 1465, 1437, 1036, 673; HRMS calcd *m*/*z* for $C_{24}H_{36}N_2O_3$ 400.2725, found 400.2710.

3g-C$_{12}$MPGN: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.15−7.02 (merge with solvent), 4.32, 3.49, 3.02, 2.23, 1.40, 0.99.

Isoxazolidine 5h-exo: ^{1}H NMR was collected at 70 °C (C_6D_6, 600 MHz) δ 7.16−7.09 (merged with solvent peak), 7.12 (m, 1H) 7.09 (m, 2H), 7.03 (t, J = 7.2 Hz, 1H), 4.31 (d, J = 7.3 Hz, 1H), 4.21 (d, J = 3.4 Hz, 1H), 3.77 (d, J = 14.3 Hz, 1H), 3.58 (d, J = 14.3 Hz, 1H), 3.47 (t, J = 7.3 Hz, 2H), 3.02 (dd, J = 7.3, 3.4 Hz, 1H), 1.63 (quintet, 2H), 1.29−1.27 (br, 18H), 0.90 (t, J = 7.0 Hz, 3H). For comparison, ^{1}H NMR data at room temperature are also provided here: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.16−7.12 (merged with solvent peak), 7.10 (m, 5H), 7.03 (t, J = 7.3 Hz, 1H), 4.23 (br, 1H), 3.73 (d, J = 14.4 Hz, 1H), 3.50−3.47 (a doublet at 3.50, J = 14.4 Hz, ^{1}H merged together with a triplet, J = 6.4 Hz, 2H), 2.93 (dd, J = 7.3, 3.4 Hz, 1H), 1.63 (br, 2H), 1.28−1.25 (br, 18H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (600 MHz, C_6D_6) δ 175.1 (2C), 137.3, 136.9, 128.9 (2C), 128.7 (2C), 128.5 (2C), 128.4 (2C), 127.9, 127.5, 76.2, 71.7 (br), 57.1 (br, 2C), 39.1, 32.3, 30.10, 30.08 (2C), 30.05, 29.9, 29.6, 27.9, 27.1, 23.1, 14.4; FT-IR (dropcast on NaCl, cm^{-1}) ν 2926, 2854, 1711, 1496, 1455, 1438, 1399, 1366, 1156, 1069, 1044, 850, 760, 745, 730, 698, 626; HRMS calcd *m*/*z* for $C_{30}H_{40}N_2O_3$ 476.3039, found 476.3043.

Isoxazolidine 5h-endo: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.28 (d, J = 7.6 Hz, 2H), 7.14−7.10 (merged in the solvent peak, 6H), 7.05−7.00 (m, 2H), 4.01 (d, J = 7.4 Hz, 1H), 3.93 (d, J = 15.4 Hz, 1H), 3.54−3.34 (t, a doublet at 3.54, J = 15.4 Hz, 1H, merged with another doublet 3.52, J = 8.5 Hz, 1H), 3.34 (t, J = 7.7 Hz, 2H), 2.74 (dd, J = 7.4, 8.5 Hz, 1H), 1.24 (br, 20H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, C_6D_6) δ 174.5, 172.2, 136.4, 134.6, 128.87 (4C), 128.77, 128.42 (2C), 127.90 (2C), 127.48, 76.4, 74.2, 58.3, 53.8, 38.9, 32.3, 30.1, 30.1, 30.0, 29.98, 29.81, 29.59, 28.2, 27.3, 23.1, 14.4; FT-IR (dropcast on NaCl, cm^{-1}) ν 2926, 2855, 1714, 1499, 1956, 1437, 1399, 1373, 1347, 1261, 1162, 1082, 1030, 870, 756, 732, 698; HRMS calcd *m*/*z* for $C_{30}H_{40}N_2O_3$ 476.3039, found 476.3038.

3h-C$_{12}$MPGN: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.26−7.00 (merge with solvent), 4.45, 4.30, 3.97, 3.74, 3.58−3.34, 3.03, 1.39, 0.97.

Isoxazolidine 5i-exo: ^{1}H NMR was collected at 70 °C (C_6D_6, 600 MHz) δ 6.71 (br, 1H), 6.56 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 5.37 (d, J = 1.3 Hz, 1H), 5.34 (d, J = 1.3 Hz, 1H), 4.29 (d, J = 7.2 Hz, 1H), 3.84 (br, 1H), 3.45 (t, J = 7.3 Hz, 2H), 2.99 (dd, J = 7.2, 4.0 Hz, 1H), 2.27 (s, 3H), 1.61 (quintet, 2H), 1.28−1.25 (br, 18H), 0.90 (t, J = 7.0 Hz, 3H). For comparison, ^{1}H NMR data at room temperature 25 °C are also provided here: ^{1}H NMR (C_6D_6, 600 MHz) δ 6.56 (d, J = 7.8 Hz, 1H), 5.31 (d, J = 1.3 Hz, 1H), 5.27 (d, J = 1.3 Hz, 1H), 4.20 (br, 1H), 3.45 (br, 2H), 2.90 (dd, J = 7.3, 3.6 Hz, 1H), 2.22 (br, 3H), 1.60 (br, 2H), 1.28−1.22 (br, 18H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (600 MHz, C_6D_6) δ 175.15, 175.10, 148.50, 148.17, 122.4, 108.4 (br, 2C), 101.22 (2C), 76.1 (br, 2C), 57.3 (br, 2C), 39.0, 32.3, 30.1 (2C), 29.99, 29.92, 29.80, 29.48, 27.94, 27.03, 23.1, 14.4; FT-IR (dropcast on NaCl, cm^{-1}) ν 2925, 2854, 1711, 1505, 1491, 1445, 1400, 1370, 1348, 1251, 1191, 1099, 1039, 932, 840, 810, 788, 718, 668, 606, 562; HRMS calcd *m*/*z* for $C_{25}H_{36}N_2O_5$ 444.2624, found 444.2615

Isoxazolidine 5i-endo: ^{1}H NMR (C_6D_6, 600 MHz) δ 6.71 (d, J = 1.6 Hz, 1H), 6.65 (dd, J = 1.6, 7.9 Hz, 1H), 6.54 (d, J = 1.6, 7.9 Hz, 1H), 5.21 (2d, J = 4.8 Hz, 2H), 4.06 (d, J = 7.4 Hz, 1H), 3.39 (t, J = 7.3 Hz, 2H), 3.14 (d, J = 8.6 Hz, 1H), 2.76 (dd, J = 7.4, 8.6 Hz, 1H), 2.35 (s, 3H), 1.59 (quintet, 2H), 1.27 (br, 18H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, C_6D_6) δ 174.6, 172.4, 148.5, 148.3, 121.7, 114.1, 108.5, 108.3, 101.2, 76.4, 75.3, 54.4, 42.3, 39.0, 32.3, 30.10, 30.08, 30.03, 29.92, 29.80, 29.54, 28.3, 27.3, 23.1, 14.4; FT-IR (dropcast on NaCl, cm^{-1}) ν 2924, 2854, 1710, 1505, 1489, 1465, 1445, 1369, 1348, 1251, 1173, 1099, 1038, 934, 861, 811, 718, 627; HRMS calcd *m*/*z* for $C_{25}H_{36}N_2O_5$ 444.2624, found 444.2619.

3i-C$_{12}$MPGN: ^{1}H NMR (C_6D_6, 600 MHz) δ 6.69, 6.56, 5.33, 4.27, 3.51, 3.14, 2.40, 2.25, 1.39, 0.98.

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Supporting Information Available: General experimental details, details of the synthesis and characterization of C_{12}MPGN, **1**-C_{12}MPGN and **2**-C_{12}MPGN and **4**, ^{1}H NMR spectra of C_{12}-MPGN, **1**-C_{12}MPGN and **2**-C_{12}MPGN, **3(a−i)**-C_{12}MPGN and ^{1}H and ^{13}C NMR spectra **5(a−i)**. Other characterization details such as TEM. This material is available free of charge via the Internet at http://pubs.acs.org.

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