Facile Functionalization of Gold Nanoparticles via Microwave-Assisted 1,3 Dipolar Cycloaddition

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This contribution describes a simple and facile method for the functionalization of thiol-coated gold nanoparticles using microwave-assisted 1,3 dipolar cycloadditions. The developed procedure allows for the attachment of terminal alkynes onto azide-containing gold nanoparticles in nearly quantitative conversions within minutes. The utility of the method has been demonstrated by attaching a library of substituted alkynes onto gold nanoparticles in nearly quantitative yields. In a proof of principle study, we demonstrate the potential use of this methodology in catalysis by attaching palladium catalysts to the azide-containing gold nanoparticles and investigate the resulting materials as supported catalysts in Suzuki couplings. Activities that rival the nonsupported analogues were observed, demonstrating that the nanoparticle support does not interfere with the catalytic activity.

Gold nanoparticles are among the most studied metallic nanoparticles because they have the potential to play an important role in catalysis, imaging, disease diagnostics, and gene expression.[1−8] Biotechnology is one area where gold nanoparticles have been identified as interesting materials.[1,4,5,9,10] For example, the grafting of carcinoembryonic antigen antibodies onto gold nanoparticles followed by the immobilization of the functionalized particles onto a gold electrode enhances the selectivity of immunoassay electrodes.[11] A second application of gold nanoparticles is in catalysis. One interesting report in this area describes the use of *N*-imidazole-functionalized thiolate gold nanoparticles for the cleavage of 2,4-dinitrophenyl acetate.[7,12] The underlying methodology that is crucial to these applications is the easy, high-yielding functionalization of gold nanoparticles with any compound of interest. Unfortunately, such modification methodologies for gold nanoparticles are scarce and remain a challenge for scientists, presenting a roadblock for further research. Herein, we present a straightforward functionalization strategy to overcome these shortcomings using 1,3 dipolar cycloadditions.

Our methodology is based on the synthesis of alkylthiol-protected gold nanoparticles using phase-transfer chemistry developed by Brust et al.[13,14] The Brust strategy allows for full control over the size and solubility of the particles and has been employed in the synthesis of alkylthiol monolayer-protected gold nanoparticles using a library of alkanethiolates.[2,6,7,15−17] Furthermore, it was demonstrated that alkyl thiols can be exchanged on the gold nanoparticles, allowing for the introduction of functionalized thiols into the alkythiol monolayer of these gold nanoparticles[15] by simply stirring a solution of the desired functionalized thiols with the gold nanoparticles for extended periods.[13,18−20] Unfortunately, this method lacks any control during the exchange process. The ideal functionalization strategy should allow for full control during the functionalization step under mild reactions conditions (i.e., the use of a click chemistry-like reaction[21]) without the tedious synthesis of thiolated ligands. Herein, we suggest that a strategy based on the copper-catalyzed 1,3 dipolar cycloaddition fulfills this requirement.

The 1,3 dipolar cycloaddition combines an alkyne and an azide to form a triazole ring.[22] In 2002, Tornøe and Sharpless independently reported copper-catalyzed versions that often result in quantitative yields under very mild reaction conditions.[23,24] Since then, copper-catalyzed 1,3 dipolar cycloadditions have been reported as the functionalization step or main synthesis strategy for a variety of materials ranging from polymers to peptides.[25−27] It has also been recognized as an important tool

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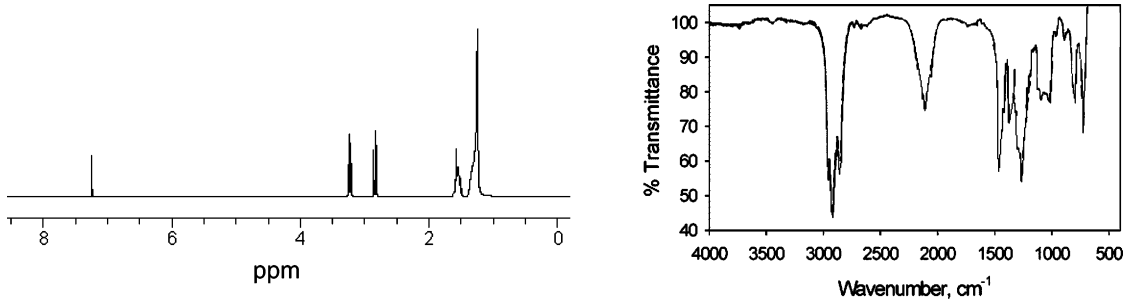
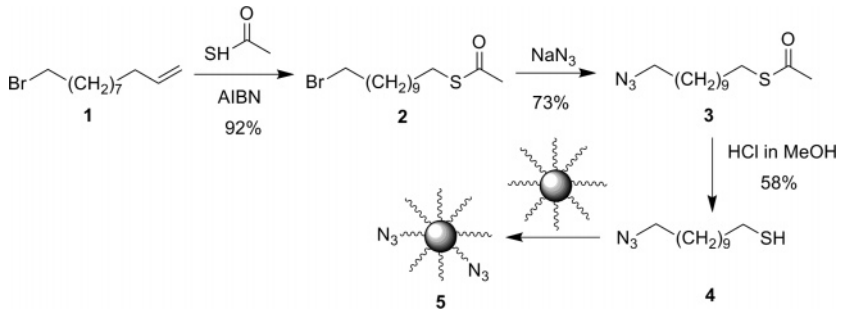


Figure 1. ^{1}H NMR spectrum of the organic compounds cleaved off of **5** and FTIR spectrum of the azide-functionalized nanoparticles.

Scheme 1. Synthesis of the Azide-Functionalized Gold Nanoparticles



in gold nanoparticle functionalization. In 2006, Fleming et al. reported the functionalization of gold nanoparticles with thiols bearing azides.[28] Although this contribution was an important step forward, it was limited to the use of activated ethynyl compounds while requiring long reaction times (24−96 h) and resulted in low yields of the desired products. Brennan et al. reported a similar method using the standard "Sharpless conditions" to introduce lipases onto gold nanoparticles.[29] However, long reaction times (96 h), a 10^6 molar excess of catalysts in comparison to the azide, and extensive purifications to remove the excess alkyne and catalyst limited the applicability of the procedure. Although these contributions demonstrate the potential of 1,3 dipolar cycloadditions in nanoparticle functionalization, a general functionalization scheme that allows for fast, quantitative attachment of any compound onto gold nanoparticles in a modular fashion is still an unfulfilled goal. In this letter, we introduce such a methodology by describing a general, high-yielding recipe to react a library of alkynes with alkylthiol-functionalized gold nanoparticles. The yields of all transformations are very high, and the purification of the functionalized gold nanoparticles can be carried out via simple extraction and precipitation.

The azide-functionalized gold nanoparticle (**5**) is the key reagent in our strategy. The synthesis of **5** is described in Scheme 1. 11-Bromo-1-undecene (**1**) was reacted with thioacetic acid to give **2**,[30,31] which was reacted with sodium azide to yield thioacetic acid-*S*-(11-azidoundecyl) ester (**3**). Compound **3** was then reacted with HCl in MeOH to generate 11-azidoundecane-1-thiol (**4**),[32] which was mixed with the alkyl thiol-protected gold nanoparticle[14] to yield **5**.

The characterization of the azide-functionalized nanoparticles was carried out using transition electron microscopy (TEM) and FTIR and NMR spectroscopy. TEM images suggested that the gold nanoparticles are between 2 and 7 nm (images and histograms of size distributions displayed in Supporting Information). The presence of the azide functionality on the gold nanoparticles was confirmed by FTIR and ^{1}H NMR spectroscopy (Figure 1). The FTIR spectra displayed a stretch around 2100 cm^{-1} characteristic of the azide functionality, and the NMR spectrum of **5** in $CDCl_3$ showed a signal at 3.24 ppm characteristic of the CH_2 group adjacent to the azide. Quantification of the azide loading on the nanoparticle was not possible using NMR spectroscopy because of the broadness of all signals and the subsequent problems with the integration of overlapping signals. Therefore, we cleaved the alkane thiols off of the gold nanoparticles by reacting the particles with I_2.[33,34] The resulting "free" alkyl thiols were then analyzed via ^{1}H NMR spectroscopy by integrating the terminal methyl group of the alkanethiols and the CH_2 group adjacent to the azide, resulting in an azide loading of 38 ± 2% (error based on the error range of ^{1}H NMR spectroscopy).

Next, the 1,3 dipolar cycloaddition of the azide-functionalized nanoparticles was investigated using a library of alkynes. First, to ensure the stability of the gold nanoparticles under reaction conditions, a test reaction was carried out with **5** using the standard 1,3 dipolar cycloaddition reaction conditions: a solvent mixture of DMSO, ^{t}BuOH, and H_2O and a catalyst mixture of 20 mol % $CuSO_4$ and 40 mol % sodium ascorbate.[22] To minimize reaction times, we employed a microwave reactor as the reaction vessel. The use of microwave-assisted 1,3 dipolar cycloadditions has been reported in the literature to shorten reaction times to 5−10 min while optimizing yields.[27,35−37] The reaction was carried out for 10 min in the microwave reactor with a reaction vessel shut off temperature of 100 °C. (Temperature control was not possible

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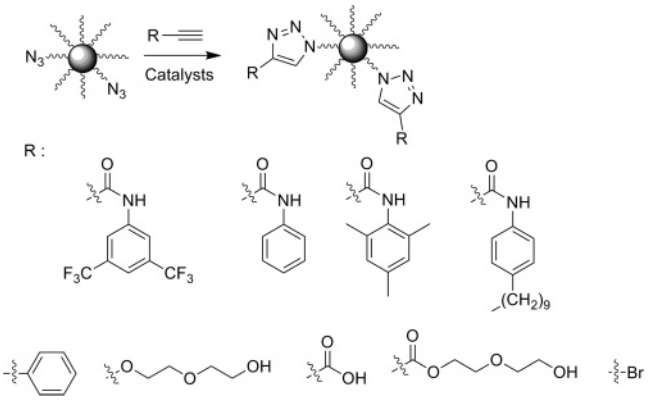
Table 1. Optimization of 1,3 Dipolar Cycloaddition Conditions for Gold Nanoparticle Functionalization Using Phenylacetylene as a Substrate

entry	$CuSO_4$ loading (mol %)	NaAsc loading (mol %)	power setting (W)	reaction time (min)	shut-off temp. (°C)	solvent mixture	yield (%)
1	1	2	100	3	50	dioxane/^{t}BuOH/H_2O:1/1/0.5	0
2	5	10	100	3	50	dioxane/^{t}BuOH/H_2O:1/1/0.5	45
3	10	20	100	3	50	dioxane/^{t}BuOH/H_2O:1/1/0.5	74
4	5	10	100	5	50	dioxane/^{t}BuOH/H_2O:1/1/0.5	77
5	5	10	150	3	50	dioxane/^{t}BuOH/H_2O:1/1/0.5	75
6	5	10	150	5	50	dioxane/^{t}BuOH/H_2O:1/1/0.5	75
7			100	3	100	dioxane/^{t}BuOH/H_2O:1/1/0.5	0
8	5	10	100	3	100	dioxane/^{t}BuOH/H_2O:1/1/0.5	82
9	10	20	100	3	100	dioxane/^{t}BuOH/H_2O:1/1/0.5	88
10	10	20	100	10	100	dioxane/^{t}BuOH/H_2O:1/1/0.5	100
11	1	2	100	10	100	THF	55
12	5	10	100	10	100	THF	82
13	10	20	100	10	100	THF	100
14	5	10	100	20	100	THF	78
15	5	10	100	20	100	THF	71

Scheme 2. Library of Alkynes Used as Substrates in the 1,3 Dipolar Cycloadditions and the Functionalized Nanoparticles before and after the Transformation



during the microwave-assisted reaction. The microwave reactor was programmed to shut down at 100 °C, which was not reached during any reactions studied.) After the reaction, **5** was characterized using FTIR and NMR spectroscopy and TEM to investigate whether any decomposition took place or any undesired side reactions occurred. The gold nanoparticles showed no changes when investigated by any of these characterization methods demonstrating the stability of gold nanoparticles under our reaction conditions (Supporting Information). A noticeable nanoparticle decomposition through particle aggregation was observed when the particles were treated for periods in excess of 15 min.

Next, the reaction protocol for the gold nanoparticle functionalization was optimized. To determine the best reaction conditions for the functionalization of **5** via 1,3 dipolar cycloadditions, we employed phenylacetylene as the alkyne of choice. The catalyst loading, reaction time, and temperature were varied during the optimization process. The solvent mixture of ^{t}BuOH and water, typically used for 1,3 dipolar cycloadditions, was not the ideal choice for our studies because of the limited solubility of the gold nanoparticles in these solvents. Therefore, we evaluated a variety of solvent mixtures. The optimization experiments are described in detail in Table 1. To characterize the yields of all reactions, the thiols were cleaved off of the nanoparticle using I_2, and the organic residues were analyzed via mass spectrometry and ^{1}H NMR spectroscopy by quantifying the disappearance of the signal at 3.24 ppm and the appearance of a new signal at 4.20 ppm that is characteristic of the methylene group located next to the newly formed triazole ring. The optimal conversions for phenylacetylene were determined to be 10 mol % $CuSO_4$, 20 mol % sodium ascorbate, a mixture of dioxane, ^{t}BuOH, and H_2O or THF as solvents, and 10 equiv of phenylacetylene (entries 10 and 13 in Table 1). Purification of the functionalized gold nanoparticles was straightforward. The addition of methylene chloride to the reaction mixture induced a phase separation between the organic layer and the aqueous layer. The organic layer was separated, the solvent was evaporated, and the gold nanoparticle residues were precipitated several times into methanol to ensure the full removal of excess alkyne.

After determining the optimal reaction conditions for the functionalization of gold nanoparticles, the versatility of the

Scheme 3. Synthesis of the Palladium Complex-Supported Gold Nanoparticles

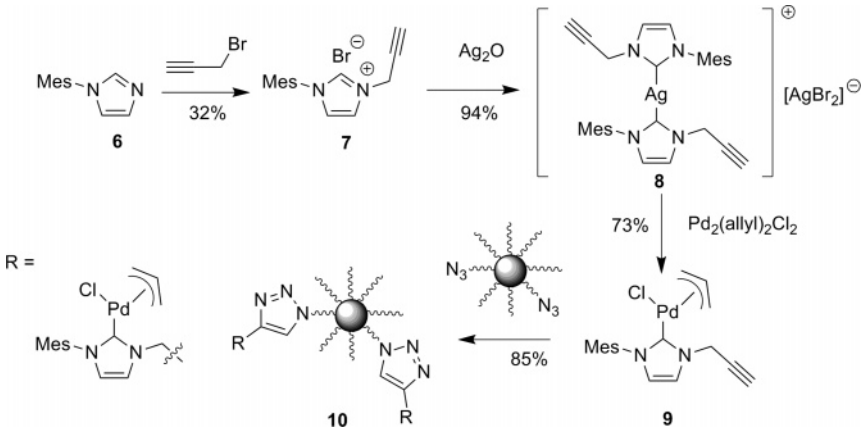
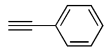
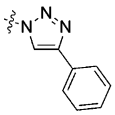
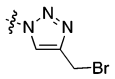
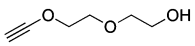
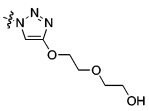
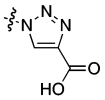
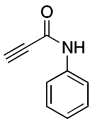
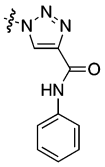
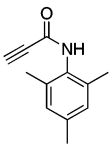
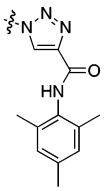
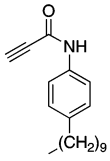
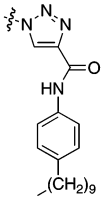
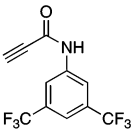
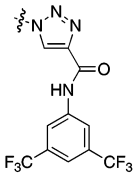
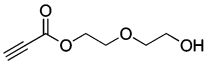
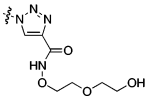


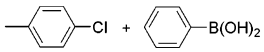
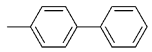
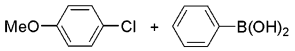
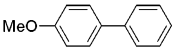
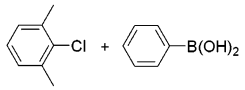
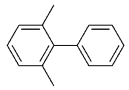
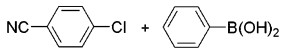
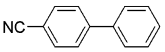
Table 2. Substrates, Products, Catalyst Loadings, and Yields of 1,3 Dipolar Cycloadditions on Gold Nanoparticles

Entry	Substrate	Product	$CuSO_4$ Loading (mol%)	Yield (%)
16			10	100
17			5	98
18			15	78
19			5	89
20			5	94
21			5	85
22			5	92
23			5	97
24			10	81

transformation using a library of alkynes was investigated. The alkynes that were employed for this study are shown in Scheme 2 and include both aromatic and aliphatic alkynes.

The results from the different nanoparticle functionalizations are described in Table 2. All experiments were carried out in THF. In general, with yields ranging from 78 to 100%, highly activated alkynes are more reactive, requiring less catalyst loading and time than their less or nonactivated analogues. Although different catalyst loadings were needed for different alkynes, we were still able to determine a general recipe for each "family" of functionalities. For aromatic alkynes, 10 mol % $CuSO_4$ and 20 mol % sodium ascorbate are required. In contrast, for alkyl-based alkynes, only 5 mol % $CuSO_4$ and 10 mol % sodium ascorbate are required for nearly quantitative conversions. However, when heteroatoms such as oxygen are adjacent to the alkyne, higher catalyst loadings are needed but only moderate to good yields are observed. In comparison, activated alkynes, such as propiolamide, require only 5 mol % $CuSO_4$ and 10 mol % sodium ascorbate to yield quantitative conversions.

Table 3. Results of the Suzuki−Miyaura Reaction Using 10

Entry	Substrates	Product	Yield
25			99%
26			99%
27			85%
28			88%

Using this newly developed synthesis protocol, we investigated the possibility of using gold nanoparticles as a support for homogeneous catalysis by adding an organometallic complex onto the gold nanoparticles as a proof of principle for the applicability of our methodology. The immobilization of well-known catalysts onto supports often facilitates the recycling and reuse of these catalysts. We previously investigated the catalytic activities of several polymer-supported catalysts containing Pd-*N*-heterocyclic carbene complexes.[38] The intrinsic characteristics of gold nanoparticles, such as tunable (i) solubility in common organic and aqueous solvents and (ii) size of the particle, make this system interesting as a potential support in catalysis. We decided to attach *N*-heterocyclic carbene (NHC) palladium complexes to the gold nanoparticles and to investigate the catalytic activity of the resulting supported complexes. Palladium NHC complexes are well-known catalysts for C−C coupling reactions, an important class of catalytic reactions with applications in polymer science as well as fine chemical and pharmaceutical industries.[38−40]

First, an alkyne containing an *N*-heterocyclic ligand was synthesized. *N*-Mesityl imidazole was refluxed with propargyl bromide in toluene for 16 h to yield the desired alkyne-containing NHC ligand (**7**). 1-Mesityl-3-(prop-2-ynyl)-1H-imidazol-3-ium bromide was then reacted with silver oxide to form silver complex **8**, by close analogy to literature procedures,[41] which was then treated with palladium allyl chloride to form **9**. Finally, using our newly developed methodology, **9** was attached to the gold nanoparticles with a yield of 85% using sodium ascorbate and $CuSO_4$ as catalysts.

Newly supported palladium complex **10** was then tested in the Suzuki coupling of a series of aryl chlorides with phenyl boronic acid (Table 3).

Because of the sensitivity of gold nanoparticles to heat, the catalytic transformations were carried out in a microwave reactor.[42] The power was set to 100 W for 6 min with a 100 °C shut off temperature. The catalyst loading for all catalytic transformations was 0.5 mol % (based on palladium), the base was Na^{t}OBu, and the solvent was dioxane. We observed excellent yields of 85−99% for all four test reactions, which are very similar to the yields reported in the literature for the homogeneous

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palladium *N*-heterocyclic carbene analogues.[43] These results demonstrate that our newly developed methodology can be employed to synthesize supported catalysts and that the resulting immobilized catalysts retain their activity when compared to their small-molecule analogues.

In summary, we have developed a synthetic protocol for the facile addition of different functionalities to gold nanoparticles in high yields within minutes. The versatility of the method was demonstrated with conversions of 80% or higher for the library of alkynes studied. This methodology has a variety of advantages over current gold nanoparticles functionalization methods, including (i) more flexibility for the synthesis of desired functionalities on gold nanoparticles, (ii) reduced reaction times, and (iii) easy purification methods. To demonstrate the versatility of the newly developed methodology as well as its applicability, we attached palladium NHC complexes to the gold nanoparticles and investigated their potential as catalysts for Suzuki couplings. The yields obtained for the Suzuki couplings were comparable to the ones obtained with the small-molecule analogues.

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Supporting Information Available: Experimental procedures and transition electron micrographs (TEM). This material is available free of charge via the Internet at http://pubs.acs.org.

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