

N-Heterocyclic Carbenes as a Robust Platform for Surface-Enhanced Raman Spectroscopy

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S Supporting Information

ABSTRACT: Surface-enhanced Raman spectroscopy (SERS) underpins a wide range of commercial and fundamental applications. SERS often relies on ligands, usually thiols, bound to a noble metal surface. The difficulty of straightforward thiol synthesis combined with their instability on surfaces highlights the need for alternative ligand design. We present the first example of SERS utilizing N-heterocyclic carbene ligands. A general three step synthesis is presented for functionalized NHC-CO₂ adducts. These ligands are deposited on SERS-active gold film-over-nanosphere substrates (AuFONs) in solvent-free and base-free conditions, which prevents fouling. The resulting films are found to be robust and capable of postsynthetic modifications.

Surface-enhanced spectroscopy is a versatile platform for low-concentration, nondestructive measurements of analytes ranging from heavy metals to biomarkers and proteins.^{1–3} The success of this approach relies on the extreme signal enhancement obtained by bringing the analyte in close proximity to a nanoscale roughened metal surface, usually Au or Ag.⁴ The surface enhancement, however, decays exponentially with distance from the surface, therefore highlighting the importance of chemically modifying the nanostructures to increase analyte affinity and decrease nonspecific binding.^{5,6}

Although many chemical groups interact with noble-metal surfaces, thiols are almost exclusively employed for surface functionalization agents.⁷ Their extensive use results from their strong affinity toward noble metals and their spontaneous assembly to form compact and well-characterized monolayers.^{6,8–10} The application of thiol-functionalized surfaces, however, is largely limited by (1) the stability of monolayers on the metal surface, particularly in biological settings or harsh chemical conditions,¹¹ and (2) the difficulties associated with the synthesis of stable thiols, particularly without multiple protection and deprotection steps. In order to have robust and versatile monolayer-based plasmonic sensors, alternative surface functionalization schemes are needed to address these dual shortcomings.

N-Heterocyclic carbenes (NHCs) are a highly influential class of ligands long known for their strong σ -bonds to transition metals.^{12,13} While a plethora of molecular organo-metallic complexes have been prepared with NHCs,¹⁴ only recently has it been demonstrated that NHCs form robust monolayers on crystalline gold surfaces.^{15–17} These monolayers

showed markedly greater resilience to chemical conditions than thiols, specifically extreme pHs and strongly oxidizing conditions.^{17–19} The key disadvantage of NHC ligands compared to traditional thiol based ones are the necessity of rigorously air and water free conditions to form the reactive carbene. In addition, the imidazolium precursors, anions, or bases are liable to foul surfaces. As a result, synthetic chemists have attempted to find other methods for making air stable NHC-precursors.^{16,17,19} However, to date, the synthesis of NHC-precursors with orthogonal functionalities are virtually unknown,²⁰ nor have surface-enhanced Raman spectra (SERS) from NHC-monolayers been reported.

In this paper, we provide a general method for synthesizing CO₂-adduct NHCs with orthogonal functional groups and report the corresponding NHC-SERS spectra. These NHC-CO₂ adducts are deposited on gold-film-over-nanosphere (AuFON) substrates in solvent-free and base-free conditions, which prevent fouling. The NHC films display excellent stability even when subject to harsh reactions conditions, including strong acids, bases, and reductants. The orthogonal functional groups allow for excellent SERS tags due to signals observed in the silent region of the Raman spectrum. Lastly, we utilize the chemical stability of our SERS-active NHC-films to demonstrate postsynthetic modifications of benzimidazolium NHCs films.

Carbenes, unlike thiols, must be deprotonated with a strong base prior to binding the metal surface. Deprotonation leads to counterions and other residual chemicals that may contaminate the surface, although use of an air-stable “free” carbene can counter this drawback. Crabtree and Taton developed the initial synthesis of air stable CO₂- and [HCO₃][–] adducts for NHCs,^{21,22} and Crudden and Johnson demonstrated that both versions can bind to highly ordered Au(111) surfaces.^{16,19} These adducts are advantageous when preparing functionalized surfaces, as CO₂ and H₂O are the only reaction byproducts.

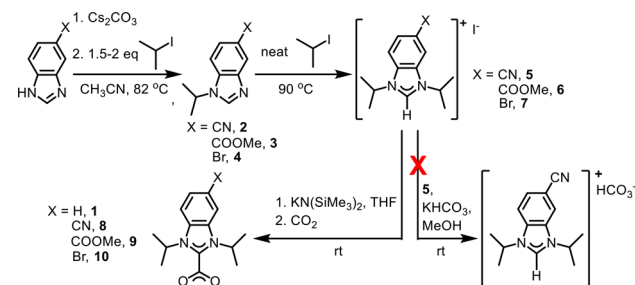
The ability to place orthogonal functional groups near a metal surface is advantageous for SERS; therefore, we synthesized four different benzimidazoliums, each with a different functional group in the 5-position employing a general two step procedure. The synthesis of 1,3-diisopropylbenzimidazolium iodide has been previously reported,²³ but other substituted examples are generally not known. Addition of cesium carbonate and 2-iodopropane to 5-cyano-1H-benzimidazole gave a mixture of 5/6-cyano-1-isopropyl-

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benzimidazole, **2**, (Scheme 1) in 92% yield. Even though two isomers were present, it was not necessary to separate them

Scheme 1. Synthesis of CO₂ Adducts of NHCs



because the compound was resymmetrized in the following reaction. 5-Cyano-1,3-diisopropyl-benzimidazolium iodide, **5**, was synthesized by addition of neat 2-iodopropane to **2** in a glass pressure tube. This tube was heated to 90 °C for 4 days and the product was recovered in 82% yield (see SI). The synthesis of the ester and bromide variants of the benzimidazoliums proceeded along the same lines as **5** (Scheme 1). The two isopropyl groups were added to 5-methyl-carboxylate-1H-benzimidazole in subsequent steps in 76% and 75% yield, respectively, to give 5-methyl-carboxylate-1,3-diisopropyl-benzimidazolium iodide, **6**. Likewise, 5-bromo-1,3-diisopropyl-benzimidazolium iodide, **7** was formed in the same two steps in 79% and 61% yield, respectively.

We first attempted to form the [HCO₃][−] adducts of the benzimidazoliums to circumvent the necessity of air-free synthesis.²¹ Stirring 1,3-diisopropyl-benzimidazolium iodide in dry KHCO₃ in anhydrous methanol led to incomplete conversion while the same reaction with **5** caused significant degradation (Scheme 1). Transient methoxide formed from either the KHCO₃ or the actual [HCO₃][−] adduct of **5** caused degradation of the nitrile to the imino ester. Though there are ways to circumvent the issue of residual unreacted iodide (i.e., addition of H₂O₂ with CO₂),¹⁹ these necessitate the use of protic solvents which would degrade electron deficient functional groups by nucleophilic attack.

To circumvent the bicarbonate adducts we directly synthesized the NHC-CO₂ adducts. 1,3-Diisopropyl-1H-benzimidazolium was deprotonated with potassium bis(trimethylsilyl)amide in THF and then CO₂ gas was added at room temperature. Addition of CO₂ caused a white powder to precipitate from solution. After washing with diethyl ether, the air-stable product, 2-carboxy-1,3-diisopropyl-benzimidazolium (**1**), was obtained in 64% yield (Scheme 1). Notably, the downfield imidazolium proton was absent in the ¹H NMR and bands at 1625 and 1369 cm^{−1} are seen in the IR, which are evidence that the CO₂ adduct has been formed (Figures S2 and S4). Compound **5** was converted into the NHC-CO₂ adduct by the same method as **1**, to give 2-carboxy-5-cyano-1,3-diisopropyl-benzimidazolium, **8**, in 77% yield. Conspicuously, **8** displays three strong stretches in the IR at 2229 cm^{−1}, for the CN, and 1614 and 1373 cm^{−1}, for the CO₂ (Figure S20). Deprotonation of **6** with potassium bis(trimethylsilyl)amide in THF followed by addition of CO₂ gas yielded 2-carboxy-5-methyl-carboxylate-1,3-diisopropyl-benzimidazolium, **9**. In the same manner as **1** and **5**, a significant CO₂ stretch is observed for **9** in the IR at 1609 and 1373 cm^{−1} and an ester stretch is found at 1721 cm^{−1} (Figure S23). The same pathway to the

bromide functionalized adduct gives **10** in 65% yield. Though compound **1** is completely stable in air, compounds **8–10** very slowly degrade under atmospheric conditions over months.

Previous work reported NHC monolayers on Au(111) surfaces, but gold surfaces lacking nanoscale roughness are not suitable for SERS.²⁴ Therefore, we developed a procedure to prepare NHC-functionalized surfaces on the well-studied gold film-over-nanosphere substrates (AuFONs). AuFONs are prepared by evaporation of gold (200 nm) on polystyrene nanospheres (600 nm diameter) using a chromium (5 nm) adhesion layer (see SI for details).²⁵ AuFONs are easily prepared and commonly employed for SERS because of their uniform enhancement factors and reproducibility.²⁶

Initially, the AuFONs were soaked in either a solution of **1** or **8** in methanol. This method, however, yielded films with a weak and irreproducible SERS response. These issues were traced to degradation of **8** in methanol. NMR of **8** for prolonged periods in CD₃OD indicates that the carboxylate on the NHC-CO₂ adduct degrades the nitrile to an imino ester. Adopting a solvent free route to film deposition avoids this dilemma. Directly placing the solid compound on the surface of the gold substrate and heating it under vacuum (5 Torr, 120 °C) provides a simple procedure for surface functionalization for all NHC-CO₂ adducts while simultaneously retaining the functional groups (Figure 1 and SI) and yields strong and

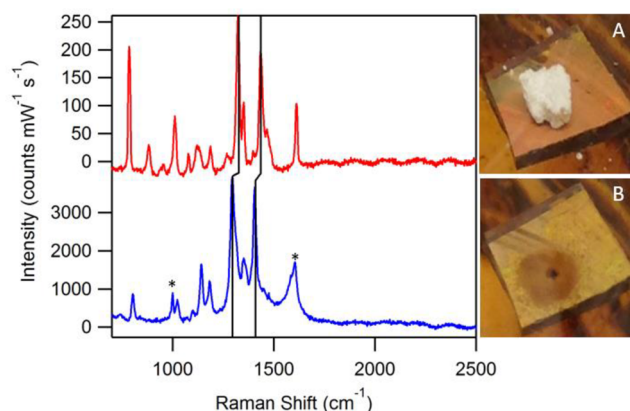


Figure 1. Raman spectrum of neat **1** (red trace) and Surface-enhanced Raman scattering spectrum (blue trace) of surface functionalized with **1**. Overlapping bands indicate the spectra are indeed of the characteristic benzimidazolium peaks, whereas much greater signal from the AuFON substrate indicates signal enhancement occurs. Asterisk (*) designates signals due to polystyrene. Panels A and B are photos taken before and after heating on the surface under vacuum, whereby **1** binds to the AuFONs.

reproducible NHC-SERS (vide infra). This solvent-free and reagent-free method prevents any inadvertent fouling of the SERS substrate by other reagents or ions.

Raman spectra of neat **1** and the SERS spectrum of AuFONs functionalized with **1** are displayed in Figure 1. Although there are differences owing to the surface-selection rules, both the Raman and SERS spectra are dominated by the strong benzimidazolium ring modes. Furthermore, binding of the carbene to the gold surface is evidenced by the consistency of our SERS bands with previously reported frequencies obtained from HREELS of NHC films in a vacuum.¹⁹ The observed red-shift (~30 cm^{−1}) of the stretching modes upon binding of the carbene to the AuFON surface is attributed to a weakening of bonds in the benzimidazolium ring as electron density is

donated from the gold surface into the ring, in contrast to the electron withdrawing nature of the CO₂ adduct (Figure S27).

We then expanded our studies to include SERS measurements of the functionalized carbenes: **8**, **9**, and **10**. Whereas Crudden reported surface plasmon resonance (SPR) measurements using NHC modified gold films, the vibrational fingerprint of individual functional groups have not been observed with NHC coated surfaces spectroscopically.²⁷ Compounds **8**, **9**, and **10** were deposited on AuFONs in the same manner as **1**, and SERS spectra were collected (Figure 2).

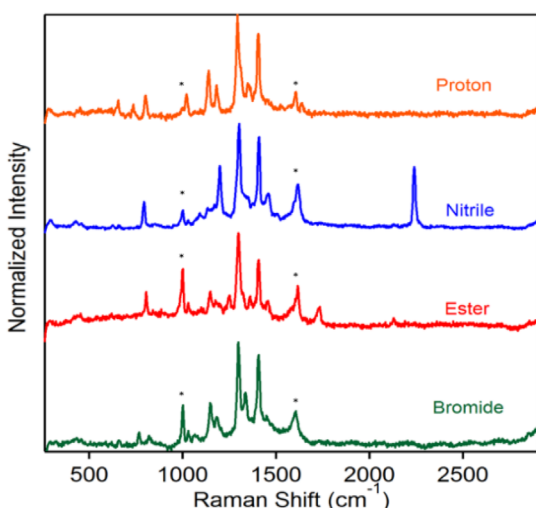


Figure 2. Surface-enhanced Raman scattering spectra of films functionalized with **1** (orange trace), **8** (blue trace), **9** (red trace), **10** (green trace). Asterisk (*) indicates contribution from polystyrene bands.

Significantly, the functional groups for the nitrile (**8**) and ester (**9**) are readily apparent in the SERS spectra at 2240 and 1720 cm⁻¹, respectively. Nitriles have been extremely useful compounds for the preparation of SERS tags due to the signal observed in the silent region of the spectrum.²⁸ These schemes, however, typically coat the particles with a metal or silica shell in order to achieve stability.²⁹ The inherent stability of carbenes on gold (discussed below) allows for a simpler synthesis of effective SERS tags that are bright in this silent region. Not surprisingly, the spectra for the bromide functionalized NHC (**10**), has signals that almost overlay **1**.

For NHCs to supplant thiol coated surfaces for SERS, they must show excellent stability under a variety of conditions. Slides with **1**-AuFONs were immersed in a variety of solvents, as well as acid and base for 24 h at room temperature. In each case, no degradation was observed (Figure S28). The resistance to acid (1 M) and base (5 M) is particularly important for postsynthetic modification at a surface and detection applications in extreme environments. Remarkably, **1**-AuFON was stable to a reductant, as exposure to a 1% solution of NH₂OH showed no degradation (Figure S30).

Postsynthetic modification allows for building successive complex compounds on a surface or solid that may otherwise be highly challenging or unfeasible.^{24,30} Postsynthetic modification of **9**-AuFON is an excellent test case because the alkyl functionality of the ester can be removed to give the carboxylate that would be challenging to synthesize directly.²⁰ An IR of **9** shows the signature ester stretch at 1720 cm⁻¹. A reaction of **9**-AuFONs and excess KOH in reagent-grade 95%

ethanol showed elimination of the peak at 1720 cm⁻¹ and retention of the other peaks. In particular, a change in the relative intensities of the bands near 1100–1200 cm⁻¹ indicates hydrolysis of the ester to the carboxylate (Figure 3). This

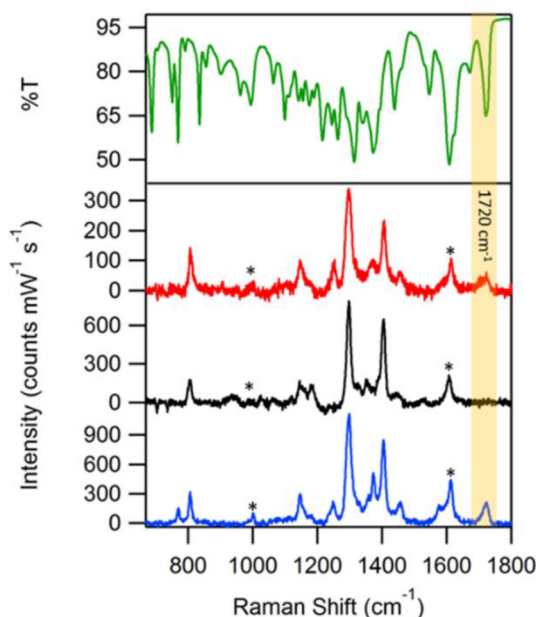


Figure 3. Reaction of carboxylate functionalized surfaces. After reaction surfaces functionalized with **9** with base (red trace to black trace), heating in a solution of EEDQ can reform the methyl ester (blue trace). Overlaid IR spectrum of **9** (green trace) corresponds to the signature ester peak. Asterisk (*) indicates contribution from polystyrene bands.

reactivity was further confirmed by reformation of the original **9**-AuFON by addition of the commonly used coupling reagent, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), in a methanol solution.³¹ This pair of reactions shows that postsynthetic modifications are possible on NHC modified surfaces for SERS applications.

In conclusion, we have demonstrated a general three step synthesis for preparing orthogonally functionalized, masked NHCs. These CO₂-adducted NHCs react in solvent free conditions under heating in vacuo on AuFONs to form NHC-functionalized substrates. The characteristic peaks from the benzimidazolium are SERS enhanced and represent the first NHC SERS spectra. Functional groups with clear vibrational modes in the silent region (such as nitrile) are easily prepared, which makes these species highly valuable as tags for a variety of SERS surfaces. The coated AuFONs are stable to a variety of solvents, acid, base, and reductants, which is in direct contrast to thiol coated AuFONs. Finally, the stability of NHC coated AuFONs allows for postsynthetic modification at the surface. These factors, from ease of synthesis for functionalized NHCs, to improved stability, demonstrate that NHC's have great potential to supplant thiols for surface-enhanced spectroscopy applications in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b12779.

Synthetic details for organic compounds, NMR spectra (^1H and ^{13}C), IR spectra, SEM images, and additional SERS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Huang, T.; Nallathamby, P. D.; Gillet, D.; Xu, X.-H. *N. Anal. Chem.* **2007**, *79*, 7708–7718.
- (2) Qian, X.; Peng, X.-H.; Ansari, D. O.; Yin-Goen, Q.; Chen, G. Z.; Shin, D. M.; Yang, L.; Young, A. N.; Wang, M. D.; Nie, S. *Nat. Biotechnol.* **2008**, *26*, 83–90.
- (3) Trujillo, M. J.; Jenkins, D. M.; Bradshaw, J. A.; Camden, J. P. *Anal. Methods* **2017**, *9*, 1575–1579.
- (4) Willets, K. A.; Van Duyne, R. P. *Annu. Rev. Phys. Chem.* **2007**, *58*, 267–297.
- (5) Malinsky, M. D.; Kelly, K. L.; Schatz, G. C.; Van Duyne, R. P. *J. Am. Chem. Soc.* **2001**, *123*, 1471–1482.
- (6) Love, J. C.; Estroff, L. A.; Kriebel, J. K.; Nuzzo, R. G.; Whitesides, G. M. *Chem. Rev.* **2005**, *105*, 1103–1170.
- (7) Sun, F.; Galvan, D. D.; Jain, P.; Yu, Q. *Chem. Commun.* **2017**, *53*, 4550–4561.
- (8) Ulman, A. *Chem. Rev.* **1996**, *96*, 1533–1554.
- (9) Schwartz, D. K. *Annu. Rev. Phys. Chem.* **2001**, *52*, 107–137.
- (10) Vericat, C.; Vela, M. E.; Benitez, G.; Carro, P.; Salvarezza, R. C. *Chem. Soc. Rev.* **2010**, *39*, 1805–1834.
- (11) Schoenfish, M. H.; Pemberton, J. E. *J. Am. Chem. Soc.* **1998**, *120*, 4502–4513.
- (12) Schuster, O.; Yang, L.; Raubenheimer, H. G.; Albrecht, M. *Chem. Rev.* **2009**, *109*, 3445–3478.
- (13) Lin, J. C. Y.; Huang, R. T. W.; Lee, C. S.; Bhattacharyya, A.; Hwang, W. S.; Lin, I. J. B. *Chem. Rev.* **2009**, *109*, 3561–3598.
- (14) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485–496.
- (15) Weidner, T.; Baio, J. E.; Mundstock, A.; Große, C.; Karthäuser, S.; Bruhn, C.; Siemeling, U. *Aust. J. Chem.* **2011**, *64*, 1177–1179.
- (16) Zhukhovitskiy, A. V.; Mavros, M. G.; Van Voorhis, T.; Johnson, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 7418–7421.
- (17) Crudden, C. M.; Horton, J. H.; Ebraldize, I. I.; Zenkina, O. V.; McLean, A. B.; Drevniok, B.; She, Z.; Kraatz, H.-B.; Mosey, N. J.; Seki, T.; Keske, E. C.; Leake, J. D.; Rousina-Webb, A.; Wu, G. *Nat. Chem.* **2014**, *6*, 409–414.
- (18) MacLeod, M. J.; Johnson, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 7974–7977.
- (19) Crudden, C. M.; Horton, J. H.; Narouz, M. R.; Li, Z.; Smith, C. A.; Munro, K.; Baddeley, C. J.; Larrea, C. R.; Drevniok, B.; Thanabalasingam, B.; McLean, A. B.; Zenkina, O. V.; Ebraldize, I. I.; She, Z.; Kraatz, H.-B.; Mosey, N. J.; Saunders, L. N.; Yagi, A. *Nat. Commun.* **2016**, *7*, 12654.
- (20) Salorinne, K.; Man, R. W. Y.; Li, C.-H.; Taki, M.; Nambo, M.; Crudden, C. M. *Angew. Chem., Int. Ed.* **2017**, *56*, 6198–6202.
- (21) Fèvre, M.; Pinaud, J.; Leteneur, A.; Gnanou, Y.; Vignolle, J.; Taton, D.; Miqueu, K.; Sotiropoulos, J.-M. *J. Am. Chem. Soc.* **2012**, *134*, 6776–6784.
- (22) Voutchkova, A. M.; Feliz, M.; Clot, E.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 12834–12846.
- (23) Chen, W.-C.; Lai, Y.-C.; Shih, W.-C.; Yu, M.-S.; Yap, G. P. A.; Ong, T.-G. *Chem. - Eur. J.* **2014**, *20*, 8099–8105.
- (24) Banholzer, M. J.; Millstone, J. E.; Qin, L.; Mirkin, C. A. *Chem. Soc. Rev.* **2008**, *37*, 885–897.
- (25) Peron, O.; Rinnert, E.; Toury, T.; Lamy de la Chapelle, M.; Compere, C. *Analyst* **2011**, *136*, 1018–1022.
- (26) Farcau, C.; Astilean, S. *J. Phys. Chem. C* **2010**, *114*, 11717–11722.
- (27) Li, Z.; Narouz, M. R.; Munro, K.; Hao, B.; Crudden, C. M.; Horton, J. H.; Hao, H. *ACS Appl. Mater. Interfaces* **2017**, *9*, 39223–39234.
- (28) Hu, Q.; Tay, L.-L.; Noestheden, M.; Pezacki, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 14–15.
- (29) Wang, Y.; Yan, B.; Chen, L. *Chem. Rev.* **2013**, *113*, 1391–1428.
- (30) Heutz, F. J. L.; Samuels, M. C.; Kamer, P. C. J. *Catal. Sci. Technol.* **2015**, *5*, 3296–3301.
- (31) Zacharie, B.; Connolly, T. P.; Penney, C. L. *J. Org. Chem.* **1995**, *60*, 7072–7074.