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Annulative π -Extension of Unactivated Benzene Derivatives through Nondirected C–H Arylation

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Supporting Information

ABSTRACT: Annulative π -extension chemistry provides a concise synthetic route to polycyclic arenes. Herein, we disclose a nondirected annulation approach of unactivated simple arenes. The palladium-catalyzed 2-fold C-H arylation event facilitates tandem C-C linkage relays to furnish fully benzenoid triphenylene frameworks using cyclic diaryliodonium salts. The inseparable regioisomeric mixture of 1- and 2-methyltriphenylenes is identified by the combined analysis of ion mobility-mass spectrometry, gas-phase infrared spectroscopy, and molecular simulation studies.



oordinating moieties on substrates guide transition-metal ✓ catalysts to proximal C−H bonds and impart site selectivity and increased reactivity.¹⁻⁴ This chelation-assisted approach promotes an effective agostic interaction between the metal center and an inert C-H bond to form an orthocyclometalation intermediate.^{1,2} C(sp²)-H activation chemistry has been utilized to provide access to extended aromatic systems such as polycyclic aromatic hydrocarbons (PAHs) and nanographene segments.⁵ Our group has previously reported a tandem arylation route using coordinating moiety-bearing arenes to obtain functionalized triphenylenes as a fully benzenoid building unit of PAHs.⁶ However, this directed annulation route, assisted by preinstalled directing groups (DGs), inevitably limits access to the parent framework structure.^{7,8} Despite recent progress on removable or traceless DG strategies including decarboxylative methods,⁹⁻¹¹ the removal of nonessential DGs is typically not trivial and can often lead to poor atom and step economy.

The symmetry, size, and structure of PAHs profoundly influence the physicochemical properties, stability, and reactivities of these frameworks.^{12–16} In particular, fully benzenoid frameworks (e.g., triphenylene, dibenzo[fg,op]tetracene, and hexa-*peri*-hexabenzocoronene) composed of Clar's aromatic sextets possess high thermodynamic stability.¹⁷ The precursors are commonly prepared by the [2 + 2 + 2] cyclotrimerization of arynes, Diels–Alder cycloaddition, or aryl–aryl cross-coupling reactions. The preassembled precursors are often stitched together through Scholl oxidation (Scheme 1a).¹² However, the complexity of prefunctionalized substrates necessitates tedious multistep procedures.

Annulative π -extension (APEX) employs one- or two-step procedures to yield DG-free PAH templates with high atom and step economy.¹⁸ In particular, edge geometrical features of the PAH templates show intrinsic reactivity toward K- or bay region-selective APEX reactions (Scheme 1b).^{18–21} However, this approach has been limited in its ability to provide fully benzenoid structures. Moreover, the substrate scaffolds possessing these peripheral features are largely based on fused-cyclic arenes and not simple arenes. Direct access to triphenylene frameworks from simple arenes presents formidable challenges associated with the (i) low reactivity of arenes and (ii) poor site-selectivity of C–H activation in the absence of DGs. Herein, we sought to devise a single-step nondirected APEX route using simple arenes for obtaining fully benzenoid triphenylenes (Scheme 1c).

Our study commenced with the nondirected approach using benzene (1a),^{22–28} which is underdeveloped as compared with the well-established directed syntheses. Cyclic diphenyliodonium salt (2a) was employed as an aryl appending agent.^{6,29–31}

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After extensive screening of palladium catalysts and reagents (see also the SI, section III), reaction conditions for the Pdcatalyzed 2-fold C–H activation relay were established to give **3aa** in 65% yield (Table 1, entry 1) under acidic conditions. In the absence of Pd(TFA)₂, TFA, or AgSbF₆, the triphenylene scaffold was not produced (entries 2–4), indicating that this nondirected APEX involves an electrophilic palladation

Ion-mobility MS: collision cross section Ion-IR spectra: vibrational wavenumber



1a 2.5 mL	+ 2a 1.0 equiv	3aa
entry	change from the standard conditions	yield ^b (%)
1	none	65 (68) ^c
2	no Pd(TFA) ₂	0
3	no TFA	0
4	no AgSbF ₆	0
5	Pd(OAc) ₂ instead of Pd(TFA) ₂	43
6	Pd ₂ (dba) ₃ instead of Pd(TFA) ₂	21
7	$Pd(MeCN)_4(BF_4)_2$ instead of $Pd(TFA)_2$	23
8	benzene (1.5 mL) + ODCB (1.0 mL)	58
9	without 3 Å MS	15
10	N ₂ atmosphere	64
11	at 110 °C	23
12	at 150 °C	38

^aStandard conditions: **2a** (0.20 mmol, 1.0 equiv), $Pd(TFA)_2$ (10 mol %), $AgSbF_6$ (0.20 mmol, 1.0 equiv), TFA (2.0 mmol, 10 equiv), **1a** (2.5 mL), 130 °C, 24 h, activated 3 Å molecular sieves (MS). ^bGC yield using *n*-dodecane as an internal standard. ^cIsolated yield. ODCB = *o*-dichlorobenzene.

event.^{32,33} Replacement of $Pd(TFA)_2$ by $Pd(OAc)_2$ resulted in a lower yield (entry 5). The catalytic activity of $Pd_2(dba)_3$ (entry 6) is presumably associated with its oxidation by hypervalent iodine reagent 2a.³⁴ Palladium complex Pd-(MeCN)₄(BF₄)₂ was not as efficient as $Pd(TFA)_2$ (entry 7). The cosolvent system of benzene and ODCB resulted in a slightly diminished yield (entry 8). The absence of molecular sieves as a drying agent led to a significantly diminished yield (entry 9), suggesting that moisture hampers the catalytic cycle. There was no significant change between air and N₂ conditions (entry 10), while both reduced and elevated reaction temperatures (entries 11 and 12) lowered the reaction yield.

Given the existing literature on Pd^{II} -catalyzed C–H arylation with hypervalent iodonium salts,³⁵ it is conceivable that the reaction of **1a** with **2a** initially affords the iodoarene intermediate shown in Scheme 2. Accordingly, the noncyclic





diphenyliodonium salt 2a' produced biphenyl (BP) under the same reaction conditions (SI section III, 88% yield). In case of cyclic 2a, the hypothetical iodoarene intermediate may then undergo oxidative addition to Pd^{II} and intramolecular C–H activation to initiate the second arylation event yielding 3aa.

Having established the optimized reaction conditions, we next focused on the substrate scope of our APEX approach (Scheme 3). Gratifyingly, substituted nonfused simple arenes bearing electron-donating alkyl groups were found to be compatible with the optimized conditions, affording the desired triphenylene products in good yields (3ba-3ha). In particular, sterically hindered isopropyl-, tert-butyl-, and cyclohexyl- substituted arenes exclusively afforded the (β + γ) arylated products (3ea-3ga), which are inaccessible by the chelating-group assisted approach. Compared with partially saturated tetralin 1j, naphthalene 1k was found to be more reactive in this transformation, presumably due to its π coordination to the active Pd species.^{36,37} Electron-rich indole 11 also underwent the annulation, even without the aid of TFA. The electron-rich ethoxy and methoxy groups were also tolerated under the reaction conditions, providing the desired triphenylene products (3ma-3oa). However, the electrondeficient arenes (1p-1r) showed low or no reactivity, which endorses the involvement of an electrophilic reaction pathway. Interestingly, unprotected benzoic acid (1q) provided the parent triphenylene (3aa) via a decarboxylative C-H arylation pathway.^{10,11} In addition, the competition experiments





^{*a*}Reaction conditions: **2** (0.20 mmol, 1.0 equiv), $Pd(TFA)_2$ (10 mol %), $AgSbF_6$ (0.20 mmol, 1.0 equiv), TFA (2.0 mmol, 10 equiv), **1** (2.5 mL), 130 °C, 24 h, activated 3 Å MS. ^{*b*}Isolated yields. ^cInseparable regioisomeric ratios are determined by ¹H NMR spectroscopy. ^{*d*}20.0 equiv of corresponding substrate in ODCB (2.5 mL). ^{*e*}30.0 equiv of corresponding substrate in ODCB (2.5 mL). ^{*f*}No TFA.

between 1n and 1a or 1p, respectively, support the involvement of an electrophilic event (SI section IV).

Encouraged by this achievement, we next explored the versatility of a series of iodonium salts 2 for the 2-fold aryl-transfer reactions. The electronic nature of cyclic iodonium salts seemed to have only a marginal effect on the yields. Symmetrical and unsymmetrical 2 are applicable to produce substituted triphenylenes (3ab-3ag) in moderate yields. Undesired dimerization of 2b was also observed to give 4b (see also the SI).



To further investigate the synthetic utility of this direct APEX protocol, we sought to apply our methodology to phenylethyl resorcinol, a commercial skin-lightening agent found in cosmetics, 38,39 due to its simple arene-based structure. To our delight, the annulated derivative **6** was exclusively obtained from methyl protected **5** in 44% isolated yield through steric control. The access to **6** by alternative/directed C-H arylation is limited.



The generation of regioisomers of triphenylenes 3ba, 3ca, 3ha, 3na, and 3pa is associated with a small discrepancy in the reactivity pattern of simple arenes. Identification of an inseparable isomeric mixture of PAHs has been an arduous task.⁴⁰ Recently, the Seeberger, Pagel, and von Helden groups demonstrated comprehensive structural analyses of small organic molecules such as a benzocaine, oligosaccharide isomers, and protein structures by using ion mobility-mass spectrometry (IM-MS) and infrared (IR) spectroscopy in the gas phase.⁴¹⁻⁴⁵ IM-MS separates molecular ions based on their collision cross sections (CCSs), enabling the differentiation of isomers with varying geometrical sizes. In this regard, we speculated that combined with molecular modeling, gas-phase IR spectroscopy of mass- and ion mobility-selected ions can allow one to confirm the structures of the triphenylene regioisomers. Thus, this combination of analytical techniques was used to identify the regioisomeric mixture in the present work. Owing to their fixed geometrical sizes, $(\alpha+\beta)$ 3ba (1methyltriphenylene (1-MeTPh)) and $(\beta + \gamma)$ 3ba (2-methyltriphenylene (2-MeTPh)) were selected as model regioisomers.

Experimental details of IM-MS and gas-phase IR spectroscopy utilized in the present work are given in the SI, section VII. The electrospray ionization (ESI) mass spectrum of a sample solution of the model regioisomer mixture (1- and 2-MeTPh) in the presence of sodium cations is shown in Figure S2a. Sodiated MeTPh monomer [MeTPh + Na]⁺ (m/z 265) and its water adduct $[MeTPh + Na + H_2O]^+$ (*m*/*z* 283) were observed at high abundance. Their arrival time distributions measured by IM-MS have nonsymmetric shapes, which can be fit to two overlapping Gaussian curves (Figure S2b, red and blue lines). This suggests the presence of two isomers which slightly differ in CCS but are not clearly resolved by our instrumental conditions. Nonetheless, CCS values of the two isomers could be determined: 95 \pm 2 Å^2 and 97 \pm 2 Å^2 for $[MeTPh + Na]^+$ and $104 \pm 2 \text{ Å}^2$ and $106 \pm 2 \text{ Å}^2$ for [MeTPh]+ Na + H_2O]⁺. Theoretical CCSs predicted from the optimized structures of sodiated 1- and 2-MeTPh species (see Table S5 and) suggest that the smaller and larger CCS values correspond to 1-MeTPh and 2-MeTPh, respectively.

To further confirm the separation of the two regioisomers by IM-MS, two small fractions of the ion mobility-separated $[MeTPh + Na + H_2O]^+$ ions (I and II in Figure S2b) were isolated and further investigated by gas-phase IR spectroscopy. As shown in Figure S2c, the IR spectra of fractions I and II are different from each other and fit well theoretical IR spectra of $[1-MeTPh + Na + H_2O]^+$ and $[2-MeTPh + Na + H_2O]^+$, respectively. As shown in the inset of Figure S2c, rings of the sodiated 1-MeTPh isomer are distorted due to steric hindrance, whereas the sodiated 2-MeTPh isomer has a flat geometry. This results in noticeable differences between the peaks corresponding to out-of-plane C-H bending vibrations in the range 700-850 cm⁻¹. Detailed IR peak assignments are given in Table S6. These results demonstrate that the regioisomeric mixture of 1-MeTPh and 2-MeTPh can be discriminated and identified by IM-MS, although our current instrumental setup is not sufficient to fully resolve these isomers.

In conclusion, we have developed the first nondirected Pdcatalyzed aromatic extension approach to construct triphenylene frameworks from simple arenes. The primary synthetic challenge associated with C-H arylation of benzene and its derivatives is the low reactivity and site-selectivity. This study

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provides the straightforward APEX route via Pd-catalytic relay involving 2-fold C—H arylation in the absence of a chelating moiety, which efficiently circumvented lengthy multistep reactions. Furthermore, we demonstrate the discrimination and identification of inseparable regioisomers using a gas-phase analytical approach based on IM-MS and molecular-ion IR spectroscopy.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b02583.

Detailed experimental procedures, analytical data, and NMR spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Neufeldt, S. R.; Sanford, M. S. Controlling Site Selectivity in Palladium-Catalyzed C–H Bond Functionalization. *Acc. Chem. Res.* **2012**, *45*, 936–946.

(2) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C-H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315–1345.

(3) Ghosh, K.; Rit, R. K.; Ramesh, E.; Sahoo, A. K. Ruthenium-Catalyzed Hydroarylation and One-Pot Twofold Unsymmetrical C-H Functionalization of Arenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 7821–7825.

(4) Huang, Z.; Lumb, J.-P. Phenol-Directed C-H Functionalization. *ACS Catal.* **2019**, *9*, 521–555.

(5) Segawa, Y.; Maekawa, T.; Itami, K. Synthesis of Extended π -Systems through C–H Activation. Angew. Chem., Int. Ed. 2015, 54, 66–81.

(6) Mathew, B. P.; Yang, H. J.; Kim, J.; Lee, J. B.; Kim, Y.-T.; Lee, S.; Lee, C. Y.; Choe, W.; Myung, K.; Park, J.-U.; Hong, S. Y. An Annulative Synthetic Strategy for Building Triphenylene Frameworks by Multiple C–H Bond Activations. *Angew. Chem., Int. Ed.* **2017**, *56*, 5007–5011.

(7) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. Efficient Palladium-Catalyzed Cyclotrimerization of Arynes: Synthesis of Triphenylenes. *Angew. Chem., Int. Ed.* **1998**, *37*, 2659–2661.

(9) Zhang, F.; Spring, D. R. Arene C-H Functionalisation Using a Removable/Modifiable or a Traceless Directing Group Strategy. *Chem. Soc. Rev.* 2014, 43, 6906-6919.

(10) Wei, Y.; Hu, P.; Zhang, M.; Su, W. Metal-Catalyzed Decarboxylative C-H Functionalization. *Chem. Rev.* 2017, 117, 8864–8907.

(11) Zhang, Y.; Zhao, H.; Zhang, M.; Su, W. Carboxylic Acids as Traceless Directing Groups for the Rhodium(III)-Catalyzed Decarboxylative C-H Arylation of Thiophenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 3817–3821.

(12) Hammer, B. A. G.; Müllen, K. Dimensional Evolution of Polyphenylenes: Expanding in All Directions. *Chem. Rev.* 2016, 116, 2103–2140.

(13) Segawa, Y.; Ito, H.; Itami, K. Structurally Uniform and Atomically Precise Carbon Nanostructures. *Nat. Rev. Mater.* **2016**, *1*, 15002.

(14) Narita, A.; Wang, X.-Y.; Feng, X.; Müllen, K. New Advances in Nanographene Chemistry. *Chem. Soc. Rev.* **2015**, *44*, 6616–6643.

(15) Feng, X.; Pisula, W.; Müllen, K. Large Polycyclic Aromatic Hydrocarbons: Synthesis and Discotic Organization. *Pure Appl. Chem.* **2009**, *81*, 2203–2224.

(16) Wu, J.; Pisula, W.; Müllen, K. Graphenes as Potential Material for Electronics. *Chem. Rev.* 2007, 107, 718–747.

(17) Wassmann, T.; Seitsonen, A. P.; Saitta, A. M.; Lazzeri, M.; Mauri, F. Clar's Theory, π -Electron Distribution, and Geometry of Graphene Nanoribbons. J. Am. Chem. Soc. **2010**, 132, 3440–3451.

(18) Ito, H.; Segawa, Y.; Murakami, K.; Itami, K. Polycyclic Arene Synthesis by Annulative π -Extension. J. Am. Chem. Soc. **2019**, 141, 3–10.

(19) Ito, H.; Ozaki, K.; Itami, K. Annulative π -Extension (APEX): Rapid Access to Fused Arenes, Heteroarenes, and Nanographenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 11144–11164.

(20) Matsuoka, W.; Ito, H.; Itami, K. Rapid Access to Nanographenes and Fused Heteroaromatics by Palladium-Catalyzed Annulative π -Extension Reaction of Unfunctionalized Aromatics with Diiodobiaryls. Angew. Chem., Int. Ed. 2017, 56, 12224–12228.

(21) Ozaki, K.; Kawasumi, K.; Shibata, M.; Ito, H.; Itami, K. One-Shot K-Region-Selective Annulative π -Extension for Nanographene Synthesis and Functionalization. *Nat. Commun.* **2015**, *6*, 6251.

(22) Chen, H.; Mondal, A.; Wedi, P.; van Gemmeren, M. Dual Ligand-Enabled Nondirected C-H Cyanation of Arenes. *ACS Catal.* **2019**, *9*, 1979–1984.

(23) Chen, H.; Wedi, P.; Meyer, T.; Tavakoli, G.; van Gemmeren, M. Dual Ligand-Enabled Nondirected C-H Olefination of arenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 2497–2501.

(24) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. Ligand-Accelerated Non-Directed C-H Functionalization of Arenes. *Nature* **2017**, 551, 489–494.

(25) Naksomboon, K.; Valderas, C.; Gómez-Martínez, M.; Álvarez-Casao, Y.; Fernández-Ibáñez, M. Á. S,O-Ligand-Promoted Palladium-Catalyzed C–H Functionalization Reactions of Nondirected Arenes. *ACS Catal.* **2017**, *7*, 6342–6346.

(26) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. Beyond Directing Groups: Transition-Metal-Catalyzed C–H Activation of Simple Arenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236–10254.

(27) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. An Efficient Organocatalytic Method for Constructing Biaryls through Aromatic C–H Activation. *Nat. Chem.* **2010**, *2*, 1044–1049.

(28) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwang, F. Y.; Lei, A. Organocatalysis in Cross-Coupling: DMEDA-Catalyzed Direct C–H Arylation of Unactivated Benzene. *J. Am. Chem. Soc.* **2010**, *132*, 16737–16740.

(29) (a) Grushin, V. V. Cyclic Diaryliodonium Ions: Old Mysteries Solved and New Applications Envisaged. *Chem. Soc. Rev.* **2000**, *29*, 315–324. (b) Merritt, E. A.; Olofsson, B. Diaryliodonium Salts: a

Organic Letters

Journey from Obscurity to Fame. Angew. Chem., Int. Ed. 2009, 48, 9052–9070.

(30) Yang, S.; Hua, W.; Wu, Y.; Hu, T.; Wang, F.; Zhang, X.; Zhang, F. Site-Selective Synthesis of Functionalized Dibenzo[*f*,*h*]quinolines and Their Derivatives Involving Cyclic Diaryliodonium Salts via a Decarboxylative Annulation Strategy. *Chem. Commun.* **2018**, *54*, 3239–3242.

(31) Yang, S.; Wang, F.; Wu, Y.; Hua, W.; Zhang, F. Synthesis of Functionalized Triphenylenes via a Traceless Directing Group Strategy. Org. Lett. 2018, 20, 1491–1495.

(32) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. Cationic Pd(II)-Catalyzed C-H Activation/Cross-Coupling Reactions at Room Temperature: Synthetic and Mechanistic studies. *Beilstein J. Org. Chem.* 2016, 12, 1040–1064.

(33) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. Cationic Pd(II)-Catalysis: C-H Activation/Suzuki-Miyaura Couplings at Room Temperature. J. Am. Chem. Soc. 2010, 132, 4978-4979.

(34) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C-H Functionalization Reactions. *Chem. Rev.* 2010, *110*, 1147–1169.

(35) (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. Room Temperature Palladium-Catalyzed 2-Arylation of Indoles. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973. (b) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. Pd(II)-Catalyzed C–H Activation/Aryl-Aryl Coupling of Phenol Esters. *J. Am. Chem. Soc.* **2010**, *132*, 468– 469. (c) Chatterjee, N.; Goswami, A. Synthesis and Application of Cyclic Diaryliodonium Salts: A Platform for Bifunctionalization in a Single Step. *Eur. J. Org. Chem.* **2017**, *2017*, 3023–3032.

(36) Hickman, A. J.; Sanford, M. S. Catalyst Control of Site Selectivity in the Pd^{II/IV}-Catalyzed Direct Arylation of Naphthalene. *ACS Catal.* **2011**, *1*, 170–174.

(37) Shibata, M.; Ito, H.; Itami, K. C–H Arylation of Phenanthrene with Trimethylphenylsilane by Pd/o-chloranil Catalysis: Computational Studies on the Mechanism, Regioselectivity, and Role of o-Chloranil. J. Am. Chem. Soc. **2018**, 140, 2196–2205.

(38) Kim, B.-S.; Na, Y.-G.; Choi, J.-H.; Kim, I.; Lee, E.; Kim, S.-Y.; Lee, J.-Y.; Cho, C.-W. The Improvement of Skin Whitening of Phenylethyl Resorcinol by Nanostructured Lipid Carriers. *Nanomaterials* **2017**, *7*, 241.

(39) Cameli, N.; Agozzino, M.; Mariano, M. Clinical and Instrumental Evaluation of the Efficacy of a New Depigmenting Agent Containing a Combination of a Retinoid, a Phenolic Agent and an Antioxidant for the Treatment of Solar Lentigines. *Dermatology* **2015**, 230, 360–366.

(40) Fatayer, S.; Poddar, N. B.; Quiroga, S.; Schulz, F.; Schuler, B.; Kalpathy, S. V.; Meyer, G.; Pérez, D.; Guitián, E.; Peña, D.; Wornat, M. J.; Gross, L. Atomic Force Microscopy Identifying Fuel Pyrolysis Products and Directing the Synthesis of Analytical Standards. *J. Am. Chem. Soc.* **2018**, *140*, 8156–8161.

(41) Warnke, S.; Seo, J.; Boschmans, J.; Sobott, F.; Scrivens, J. H.; Bleiholder, C.; Bowers, M. T.; Gewinner, S.; Schöllkopf, W.; Pagel, K.; von Helden, G. Protomers of Benzocaine: Solvent and Permittivity Dependence. J. Am. Chem. Soc. **2015**, 137, 4236–4242.

(42) Seo, J.; Hoffmann, W.; Warnke, S.; Bowers, M. T.; Pagel, K.; von Helden, G. The Impact of Environment and Resonance Effects on the Site of Protonation of Aminobenzoic Acid Derivatives. *Phys. Chem. Chem. Phys.* **2016**, *18*, 25474–25482.

(43) Mucha, E.; González Flórez, A. I.; Marianski, M.; Thomas, D. A.; Hoffmann, W.; Struwe, W. B.; Hahm, H. S.; Gewinner, S.; Schöllkopf, W.; Seeberger, P. H.; von Helden, G.; Pagel, K. Glycan Fingerprinting via Cold-Ion Infrared Spectroscopy. *Angew. Chem., Int. Ed.* **2017**, *56*, 11248–11251.

(44) Seo, J.; Hoffmann, W.; Warnke, S.; Bowers, M. T.; Pagel, K.; von Helden, G. Retention of Native Protein Structures in the Absence of Solvent: a Coupled Ion Mobility and Spectroscopic Study. *Angew. Chem., Int. Ed.* **2016**, *55*, 14173–14176.

(45) Hofmann, J.; Hahm, H. S.; Seeberger, P. H.; Pagel, K. Identification of Carbohydrate Anomers Using Ion Mobility-Mass Spectrometry. *Nature* **2015**, *526*, 241–244.