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Perspective

On-Surface Cross-Coupling Reactions

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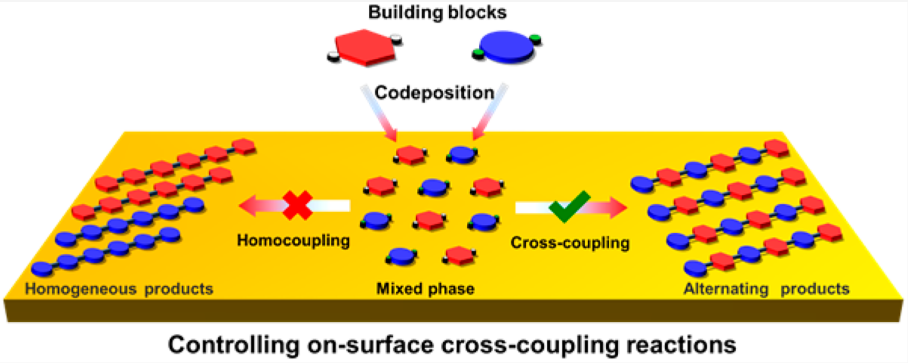

ABSTRACT: On-surface synthesis, as a bottom-up synthetic method, has been proven to be a powerful tool for atomically precise fabrication of low-dimensional carbon nanomaterials over the past 15 years. This method relies on covalent coupling reactions that occur on solid substrates such as metal or metal oxide surfaces under ultra-high-vacuum conditions, and the achievements with this method have greatly enriched fundamental science and technology. However, due to the complicated reactivity of organic groups, distinct diffusion of reactants and intermediates, and irreversibility of covalent bonds, achieving the high selectivity of covalent coupling reactions on surfaces remains a great challenge. As a result, only a few on-surface covalent coupling reactions, mainly involving dehalogenation and dehydrogenation homocoupling, are frequently used in the synthesis of low-dimensional carbon nanosystems. In this Perspective, we focus on the development and synthetic applications of on-surface cross-coupling reactions, mainly Ullmann, Sonogashira, Heck, and divergent cross-coupling reactions.

On-surface synthesis (OSS),[1] as an emerging bottom-up synthetic method, has become a powerful tool for atomically precise fabrication of low-dimensional carbon nanomaterials over the past 15 years.[2−6] It mainly involves covalent coupling reactions on solid substrates such as metal or metal oxide surfaces under ultra-high-vacuum conditions,[7,8] enabling the precise construction of diverse artificial carbon nanosystems from rationally designed precursor molecules bearing specific groups as building blocks. OSS has impressed the chemistry community with its simplicity, selectivity, and programmability during synthesis.[9] In addition, using ultra-high-spatial-resolution scientific tools such as scanning tunneling microscopy and spectroscopy (STM and STS, respectively)[10] and noncontact atomic force microscopy (nc-AFM),[11] accurate characterizations of synthesized carbon nanomaterials on surfaces have been extensively achieved at the single-molecule scale, providing in-depth insights into structure−function relationships.[6,12] For example, changing the width or edge structures of graphene nanoribbons (GNRs) changes their band gap[13−19] and engineers the topological quantum phase,[18,20−22] while increasing the length of π-conjugated polymers can drive the topological quantum phase transition.[23] The structure-related π-magnetism[17,24−29] in carbon nanosystems created using OSS has been elucidated by the combination of STM/STS, nc-AFM, and density functional theory (DFT) calculations.

In the pioneering work of the OSS field, Grill et al. first achieved on-surface Ullmann homocoupling in 2007 and demonstrated that on-surface covalent architectures are artificially programmed into one-dimensional nanowires or two-dimensional networks by changing the position of the reactive groups in the precursors and controlling the reaction hierarchy by varying the type of reactive groups.[30] Subsequently, a variety of OSS methods have been developed to generate predictable covalent structures, whether via thermal activation on catalytic metal surfaces or other types of activation on nonmetal surfaces.[7,8,31−33] These methods have enabled the production of one- and two-dimensional large carbon nano-

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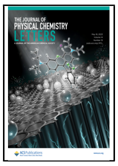

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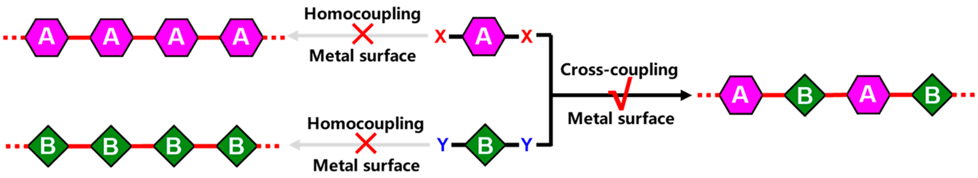

Figure 1. Controlling on-surface cross-coupling of A and B via inhibiting the homocoupling of A or B. X and Y indicate different reactive groups. The wrong and right signs on the gray and black arrows demonstrate the inhibition of homocoupling and the realization of highly selective cross-coupling, respectively.

systems with atomic precision that are inaccessible in solution due to their poor solubility.

Nevertheless, due to the complicated reactivity of organic groups, distinct diffusion of reactants and intermediates, and irreversibility of covalent bonds, achieving the high selectivity of covalent coupling reactions on surfaces remains a significant challenge. As a result, only a few on-surface covalent coupling reactions, mainly involving dehalogenation[34,35] and dehydrogenation homocoupling,[36−38] can be frequently used for the synthesis of lower-dimensional carbon nanosystems, which limits the development and application of carbon nanomaterials with specific topologies such as alternating conjugation and non-benzenoid carbon nanosystems. To expand the application of OSS in the synthesis of artificial carbon nanosystems with novel physical properties, an alternating method is the development of on-surface cross-coupling reactions, which have been demonstrated as a promising method in the synthesis of organic functional molecules in solution.[39,40] In this Perspective, we review the recent advances in the OSS field and focus on the development and synthetic applications of on-surface cross-coupling reactions, which mainly include Ullmann cross-coupling, Sonogashira and Heck reactions, and divergent cross-coupling reactions.

Cross-coupling reactions are flexible and powerful tools for constructing carbon−carbon and carbon−heteroatom bonds because they allow highly selective joining of organic moieties A and B into alternating product -A-B-A-B-, while avoiding the formation of homogeneous products -A-A-A-A- and -B-B-B-B- (Figure 1). They have been widely used to produce various organic functional molecules with alternating structures that cannot be obtained by simple homocoupling reactions. Therefore, in 2010, the Nobel Prize in Chemistry was awarded to Heck, Negishi, and Suzuki for their outstanding contributions in this field.[41] Despite their powerful applications in traditional organic synthesis, cross-coupling reactions have rarely been exploited on surfaces, where the challenges may be greater than in solution. Surfaces create heterogeneous environments where reactants can spontaneously assemble into homogeneous molecular islands, leading to “phase separation”, and the specific two-dimensional confinement effect on surfaces reduces the degree of conformational, configurational, and diffusion freedom of the reactants, which is not conducive to cross-coupling between different reactants. Therefore, to achieve highly selective cross-coupling reactions on surfaces, the following challenges need to be addressed: (1) inhibiting the homocoupling of precursor A or B, (2) improving the miscibility of precursors A and B, and (3) accelerating the cross-coupling of molecules A and B to form alternating products -A-B-A-B- (Figure 1).

Dehalogenation through Ullmann-type homocoupling is currently the most widespread method for constructing carbon−carbon bonds on surfaces, so substantial effort has been spent trying to develop Ullmann-type cross-coupling reactions including the covalent connection of two different molecules[20,42−48] and the head-to-tail covalent connection of the same dissymmetrical molecules.[21,22,49−53] In the Ullmann-type cross-coupling of two different molecules on surfaces, Kuang et al. achieved the first dehalogenation cross-coupling of aryl bromide (1) and porphyrin bromide (2) on a Au(111) surface to give polyporphyrin products with alternating benzene rings and porphyrin rings, which are not formed by homocoupling of aryl bromide (Figure 2a).[43] They ascribed the successful cross-coupling mainly to the following facts: (1) inhibition of homocoupling of rationally designed molecule 2 because of intermolecular steric hindrance involving the hydrogen atoms on the same side of bromine in planar adsorption molecule 2 and (2) greater probability of cross-coupling when the ratio of reactant 2 to reactant 1 was as high as 13:1. This strategy has been used to create graphene nanoribbon heterojunctions composed of seamlessly assembled segments of pristine graphene nanoribbons and deterministically nitrogen-doped graphene nanoribbons.[42] Recently, highly selective Ullmann-type cross-coupling reactions can also be achieved by tip-induced manipulation. Zhong et al. reported an intermolecular dehalogenation cross-coupling reaction on an insulating substrate with two-monolayer NaCl/Au(111) using STM tip-induced atom manipulation, achieving covalent connection of two different building blocks with high chemo- and regioselectivity (Figure 2b).[44] Although the tip-induced process avoids the need for thermal activation of the surface, the time-consuming nature of tip-induced processes limits its wider application.

In the Ullmann-type cross-coupling of the same dissymmetrical molecules, Di Giovannantonio et al. developed head-to-tail dehalogenation cross-coupling of aryl bromides on Au(111) using a rationally designed precursor 4,4″-dibromo-2′,3,5′-trimethyl-1,1′:4′,1″-terphenyl to construct a *para*-type oligo-(indenoindene) short chain consisting of an alternating array of five- and six-membered rings (Figure 2c).[51] They found that the neighboring methyl in the bromophenyl group inhibits its homocoupling to promote Ullmann-type cross-coupling, while the rotation of alternating methyl groups promotes the formation of target products before cyclodehydrogenation. Head-to-tail dehalogenation cross-coupling has also been used to convert 2,6-dibromoazulenes into one-dimensional covalent polymers with the continuous arrangement of pentagon−heptagon motifs,[49] which can further undergo interchain dehydrogenative fusion to form non-benzenoid graphene nanoribbons.[50] More recently, Rizzo et al. developed a head-to-tail dehalogenation cross-coupling reaction on Au(111) to fabricate sawtooth GNRs with alternating edge extensions (Figure 2d),[22] where molecular steric hindrance proved to be key to the selective formation of alternating structures. The precursor molecules adsorb on the Au(111) surface in a

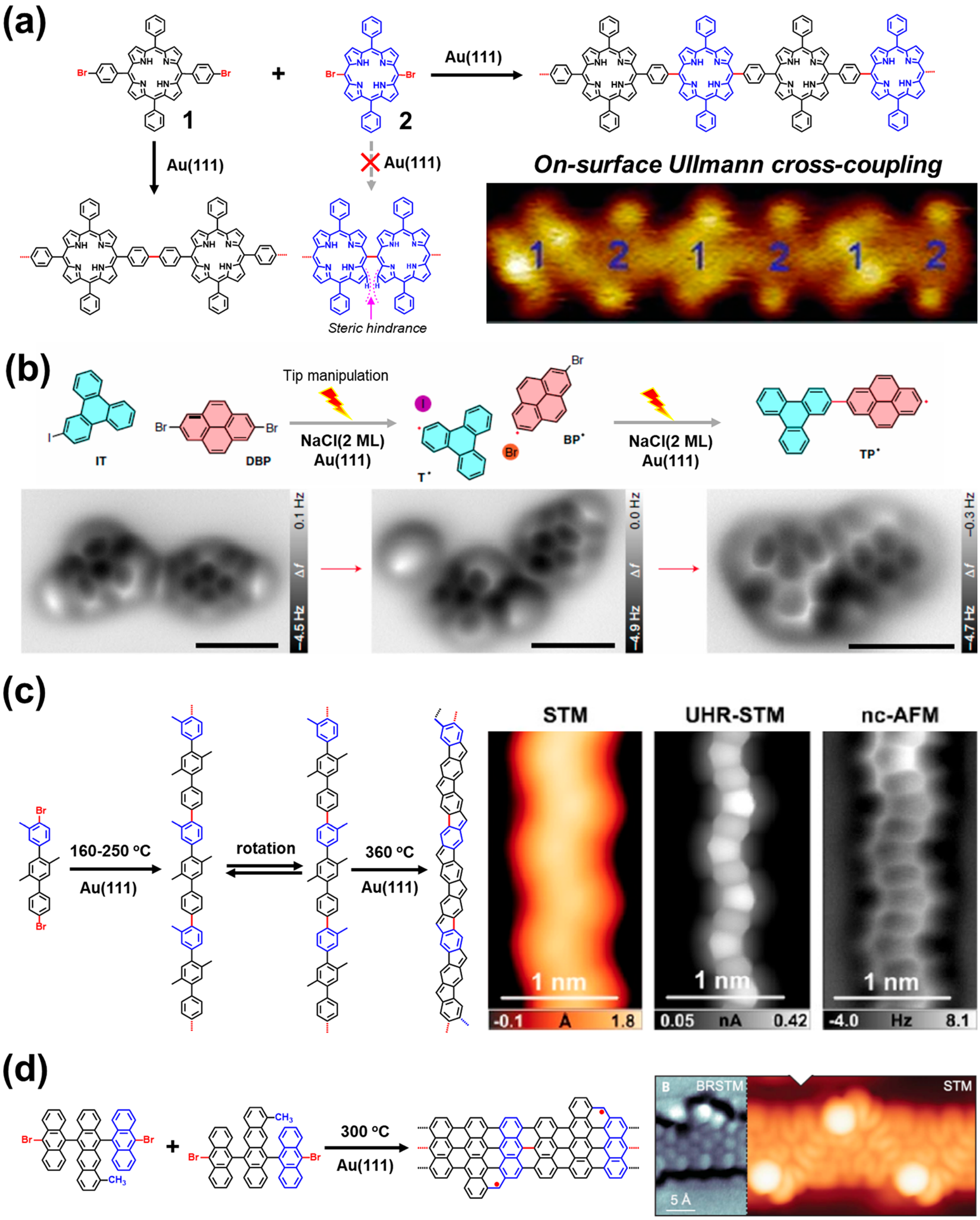

Figure 2. On-surface Ullmann cross-coupling reaction. (a) Ullmann cross-coupling of aryl bromides and porphyrin bromides on Au(111). Reproduced with permission from ref 43. Copyright 2015 John Wiley and Sons. (b) Tip-induced Ullmann cross-coupling reaction. Reproduced with permission from ref 44. Copyright 2021 Springer Nature. (c) On-surface synthesis of oligo(indenoindene) via head-to-tail Ullmann cross-coupling. Reproduced with permission from ref 51. Copyright 2020 American Chemical Society. (d) On-surface synthesis of sawtooth GNR with alternating edge extensions via head-to-tail Ullmann cross-coupling. Reproduced with permission from ref 22. Copyright 2020 American Association for the Advancement of Science.

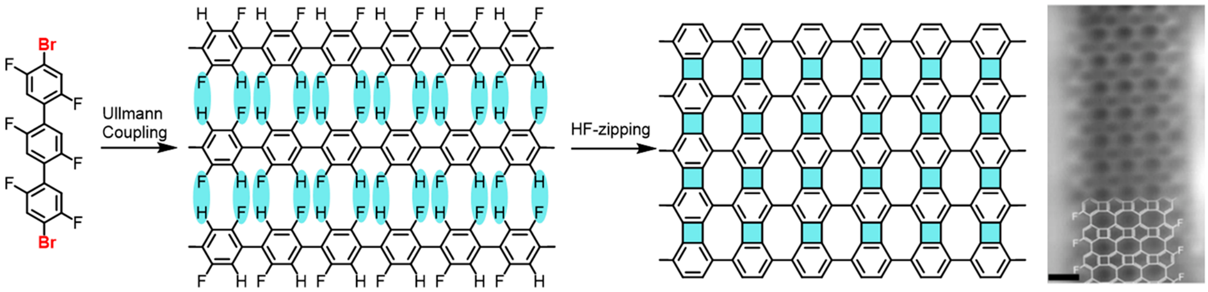

Figure 3. Synthesis of a biphenylene network on Au(111) via dehydrofluorination cross-coupling (HF zipping). Reproduced with permission from ref 54. Copyright 2020 American Association for the Advancement of Science.

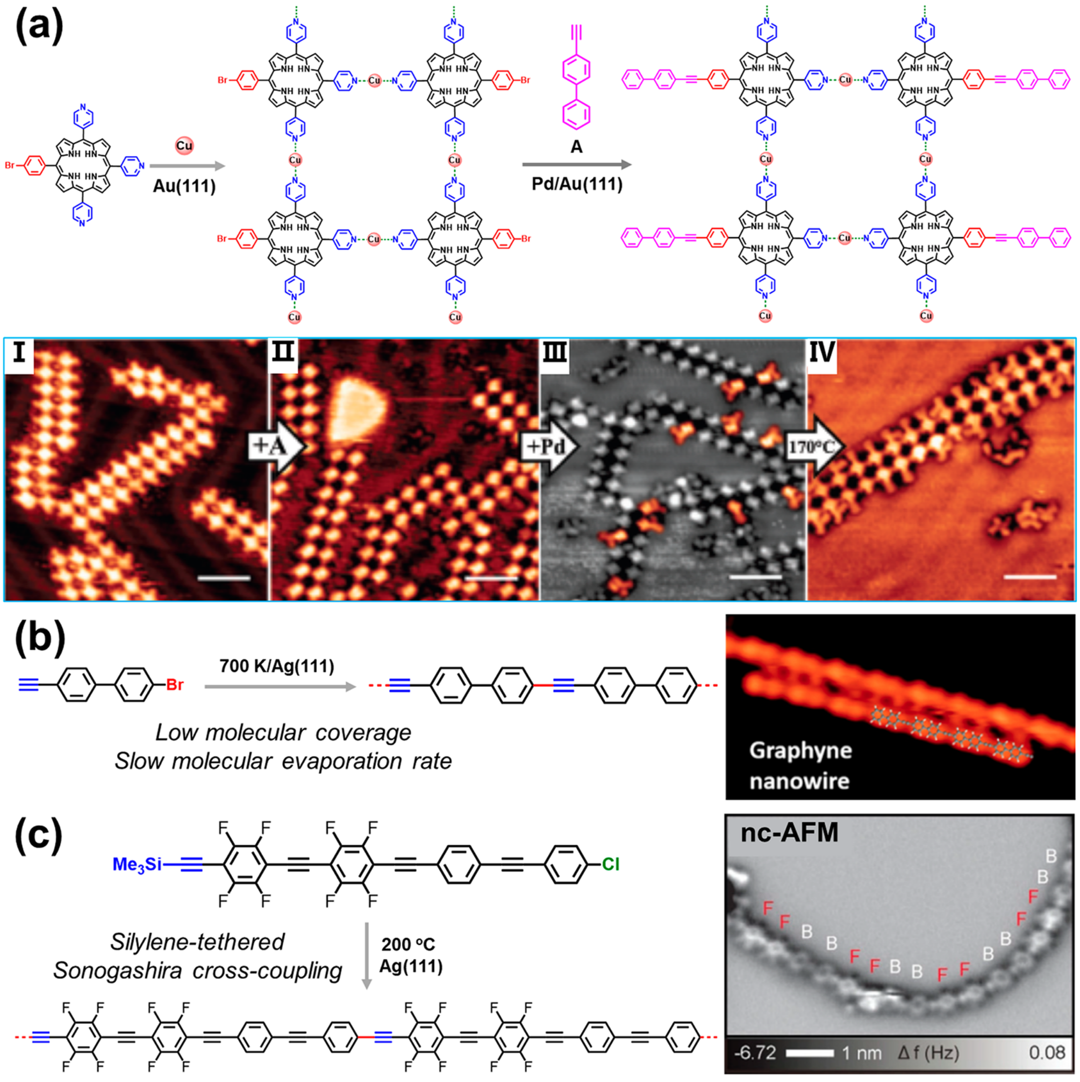

Figure 4. On-surface Sonogashira cross-coupling reaction. (a) Template-controlled Sonogashira cross-coupling on Au(111). Reproduced with permission from ref 59. Copyright 2017 Royal Society of Chemistry. (b) Formation of graphyne nanowires on Ag(111) via kinetic strategy-controlled Sonogashira cross-coupling. Reproduced with permission from ref 60. Copyright 2018 American Chemical Society. (c) Head-to-tail oligomerization via silylene-tethered Sonogashira cross-coupling. Reproduced with permission from ref 61. Copyright 2021 John Wiley and Sons.

nonplane manner mainly due to the fact that adjacent hydrogen atoms cannot get close to each other in the plane and can be attached to the surface only by alternating twists.[52] This steric effect not only affects the adsorption configuration of the molecules but also changes the way the precursor molecules approach each other. This means that the opposite distortion approach can weaken the steric effect, while the same distortion cannot approach each other.

Except for dehalogenation cross-coupling on surfaces, Fan et al. reported the formation of the biphenylene network on Au(111) by combining debromination homocoupling and interchain dehydrofluorination cross-coupling [HF zipping (Figure 3)].[54] They used 4,4″-dibromo-2,2′,2″,5,5′,5″-hexa-

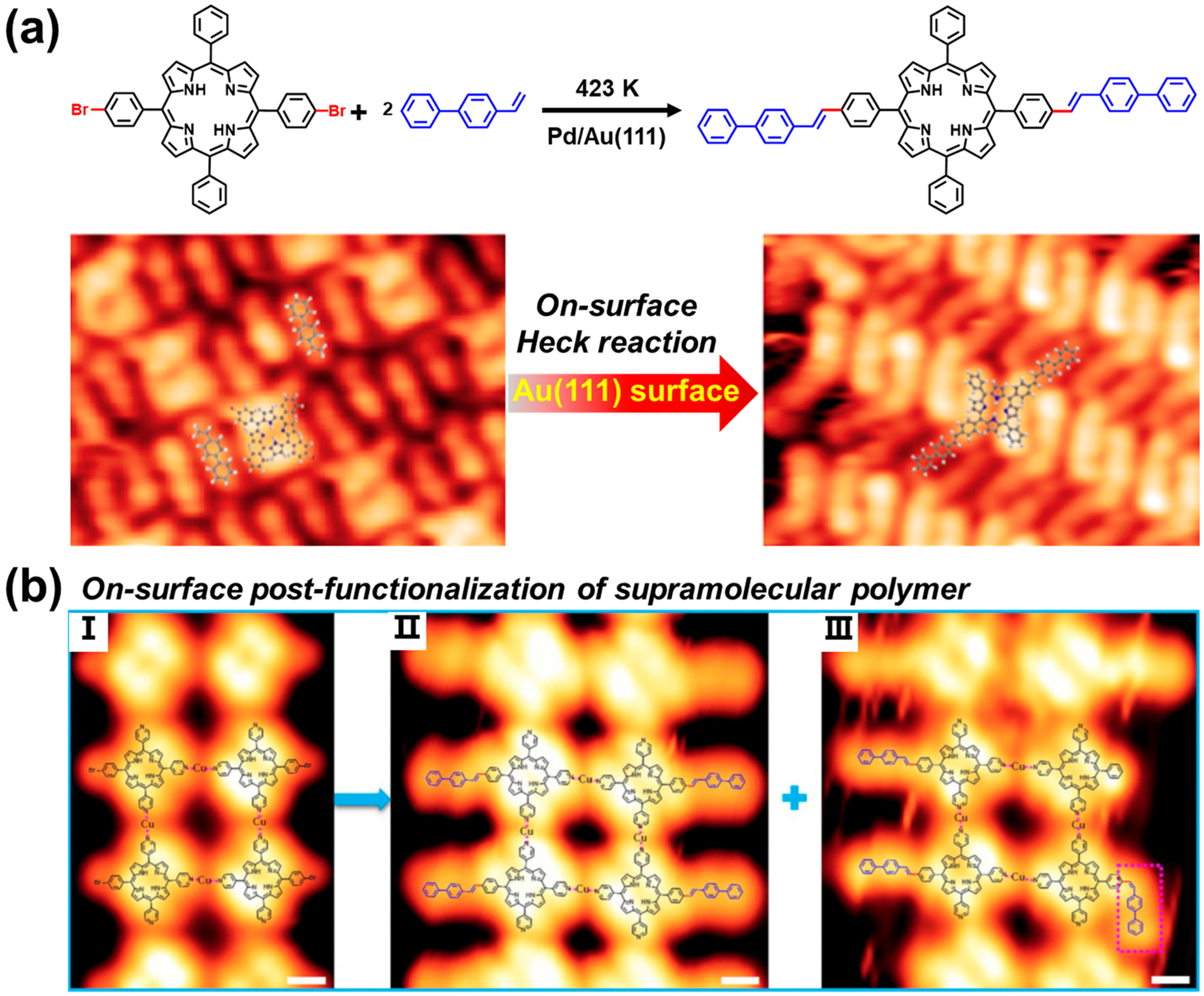

Figure 5. (a) On-surface Heck reaction of aryl bromides with alkene on Au(111) with exogenous Pd atoms as a catalyst. Reproduced with permission from ref 62. Copyright 2017 American Chemical Society. (b) On-surface postfunctionalization of supramolecular polymers via Heck reaction. Reproduced with permission from ref 63. Copyright 2021 John Wiley and Sons.

fluoro-1,1′:4′,1″- terphenyl (DHTP) as the precursor molecule, which underwent debromination homocoupling to give homochiral poly(2,5-difluoro-*p*-phenylene) (PFPP) chains on Au(111). The homochiral assembly of PFPP underwent an interchain dehydrofluorination cross-coupling to generate a two-dimensional biphenylene network.

Sonogashira cross-coupling plays an important role in the preparation of arylalkynes and conjugated enynes.[55] Under solution conditions, Sonogashira cross-coupling usually requires various additives such as ligands and basic as well as charged (ionic) species as catalysts. In 2010, Kanuru et al. reported the first Sonogashira cross-coupling of phenylacetylene and iodobenzene on an extended Au(111) surface.[56] They found that the Sonogashira cross-coupling occurred mainly on the elbows of the herringbone reconstruction on smooth Au(111), where iodobenzene and phenylacetylene could adsorb easily in the proximity of each other. In contrast, the roughened Au(111) completely inhibited cross-coupling. Subsequently, the same cross-coupling reactions were achieved on Au(100)[57] and Ag(100),[58] where the roughened Au(100) surface inhibited the phase separation and enhanced interisland contact, improving the selectivity of cross-coupling. These findings highlight the importance of the substrate for ensuring selective and efficient cross-coupling.

Templating is an important method for controlling the reaction on surfaces. Zhang et al. improved the chemoselectivity of on-surface Sonogashira cross-coupling reactions by using a metal−organic coordination template that inhibits the homocoupling of bromophenyl groups and enhances cross-coupling between bromophenyl groups and terminal alkynes.[59] In this work, the coordination of precursors 5,10,15-tris(4-pyridyl)-20-bromophenyl porphyrin and Cu adatoms on Au(111) afforded a double-row ladder template, with bromophenyl groups on both sides of the ladder (Figure 4a). Annealing at a suitable temperature in the presence of 4-ethynylbiphenyl and exogenous Pd as a catalyst led to selective cross-coupling of 4-ethynyl-1,1′-biphenyl and bromophenyl groups on both sides of the ladder. In another approach, Wang et al. reported a kinetic strategy for improving the selectivity of Sonogashira cross-coupling on Ag(111) through the synergy of a high surface temperature, a low degree of molecular coverage, and a low molecular evaporation rate (Figure 4b).[60] The low degree of coverage facilitates monomer diffusion to generate graphyne nanowires, whose formation is otherwise inhibited by steric

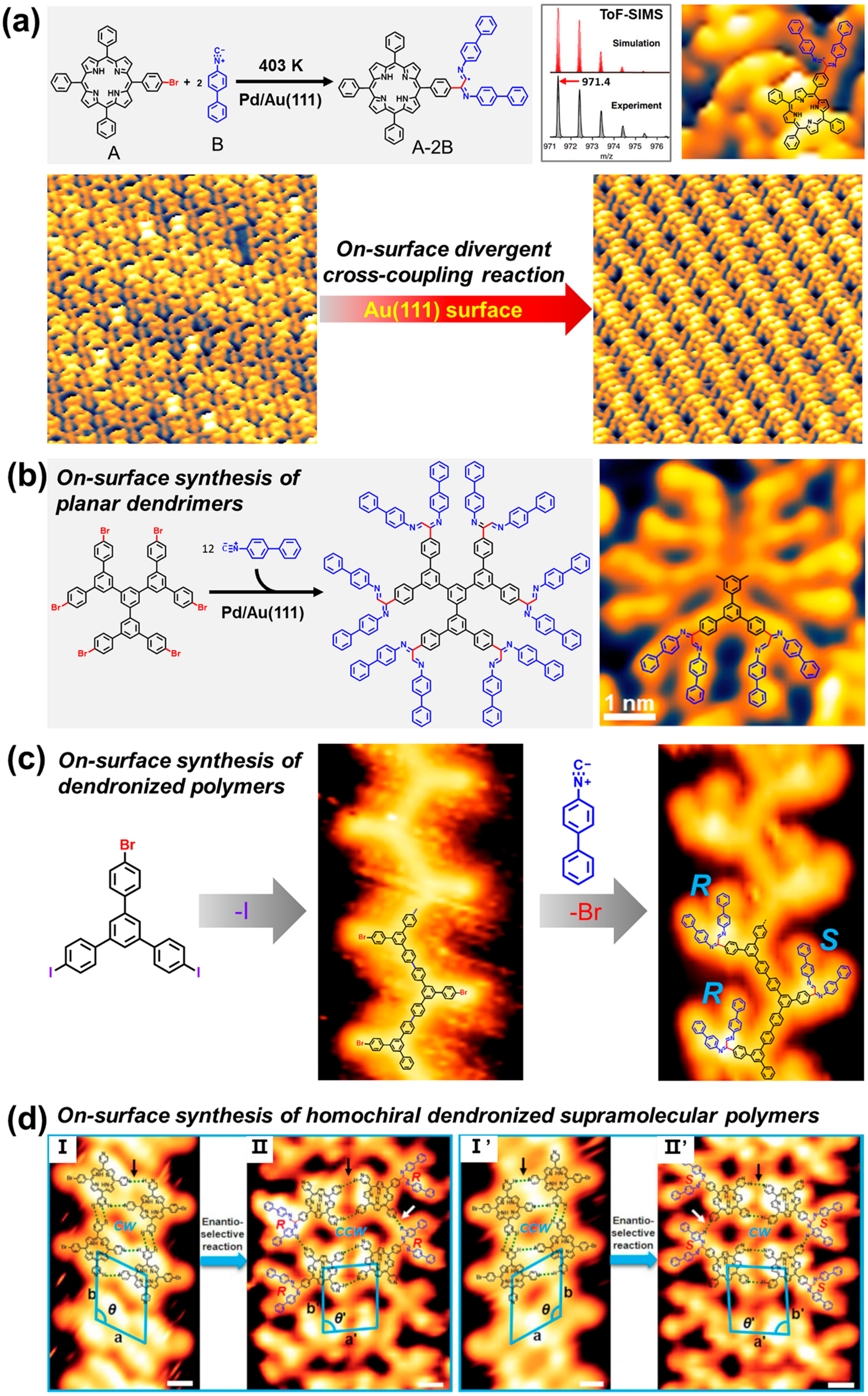

Figure 6. On-surface divergent cross-coupling reaction. (a) On-surface divergent cross-coupling of one aryl bromide with two isocyanides on Au(111). Reproduced with permission from ref 64. Copyright 2019 Springer Nature. (b) On-surface synthesis of planar dendrimers with 12 branches via divergent cross-coupling. Reproduced with permission from ref 64. Copyright 2019 Springer Nature. (c) On-surface synthesis of dendronized polymers via divergent cross-coupling. Reproduced with permission from ref 65. Copyright 2022 American Chemical Society. (d) On-surface synthesis of homochiral dendronized supramolecular polymers via enantioselective divergent cross-coupling. Reproduced with permission from ref 63. Copyright 2021 John Wiley and Sons.

hindrance when the degree of coverage is high. The high annealing temperature helps overcome the energy barrier, which is higher for Sonogashira cross-coupling than for Glaser coupling. Therefore, controlling the on-surface kinetic strategy is an efficient method for improving the selectivity of high-barrier pathways and enhancing the control of cross-coupling reactions. More recently, Sun et al. developed a desilylative Sonogashira cross-coupling reaction with high chemoselectivity of ≤75% (Figure 4c),[61] in which the high chemoselectivity is ascribed mainly to the following facts: (1) silylene tethering and (2) prior self-assembly into a linear structure with the head-to-tail connection of trimethylsilyl ethynyl and chlorophenyl groups on Ag(111) due to the partial fluorination of the precursor molecules.

Heck reaction is an important cross-coupling reaction of aryl or vinyl halides with terminal alkenes, which can be used to flexibly construct 1,2-vinylene bridge-linked molecules. Although various types of Heck reactions have been conducted in solution for many years, an on-surface Heck reaction was not reported until 2017 by Shi et al. (Figure 5a).[62] To avoid the homocoupling of aryl bromides, they developed a bimetallic catalysis strategy consisting of a Au(111) substrate and exogenous Pd adatoms. Their strategy was to use Pd atoms to decrease the reaction barrier energy of debromination and stabilize the active aryl radicals to slow homocoupling, instead of using excess alkenes to accelerate cross-coupling. Taking advantage of the on-surface Heck reaction, they further developed the postfunctionalization of supramolecular polymers to achieve the synthesis of functionalized Cu-coordinated ladder supramolecular polymers (Figure 5b).[63]

Using a bimetallic catalysis strategy, Li et al. developed a special cross-coupling on Pd/Au(111) surfaces,[64] namely on-surface divergent cross-coupling, which involves the reaction of an aryl bromide A with two isocyanides B to synthesize highly branched product A-2B with one core and two branches (Figure 6a). One of the key facets for achieving the novel reaction is the use of the isocyanide group containing two unpaired electrons at the terminal carbon, which allows the same carbon to participate in two cross-coupling reactions. Exogenous Pd atoms are critical for reducing the reaction barrier of debromination and thereby altering reaction kinetics to inhibit the homocoupling of aryl bromides. Using divergent cross-coupling, Li et al. further developed the postfunctionalization of a small molecule and a linear polymer on Au(111), achieving the precise construction of planar dendrimers (Figure 6b) and dendronized polymers with a uniform conformation and configuration (Figure 6c).[65] Notably, divergent cross-couplings have also been applied to the postfunctionalization of supramolecular polymers, in which the chiral assembly of supramolecular polymers controls the enantioselectivity of divergent cross-coupling (Figure 6d).[63] This finding provides new insight for exploring enantioselective covalent reactions on surfaces, which can be used to synthesize chiral one- or two-dimensional carbon nanosystems with unique electronic properties.

This Perspective describes several successful efforts to expand the range of on-surface cross-coupling to generate carbon nanosystems with various functional units, including highly ordered heterojunctions, sawtooth GNRs with unpaired π-electrons, a biphenylene network, planar dendrimers, and dendronized polymers, all of which would be difficult to obtain through homocoupling. The strategies for achieving a high selectivity of cross-coupling on surfaces mainly include molecular steric hindrance, templating effects involving metal coordination and substrate, exogenous metal catalysts, and the modulation of the ratio of two reactants. Although a few cross-coupling reactions have been achieved on surfaces, more effort is urgently needed to improve reaction selectivity and precisely synthesize target molecules. In particular, the studies should investigate how to improve reaction selectivity through the optimization of thermodynamics, kinetics, precursor geometry, types of reactive groups, molecular coverage on the surface, and exogenous catalysts. Expanding the toolbox of selective on-surface cross-coupling reactions will diversify the range of carbon nanomaterials that can be prepared with novel electronic, magnetic, and topological properties.

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Notes

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