ELECTROCHEMCIAL SYNTHESIS

A Gold Oxidation Relay

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Developing practical conditions for electrochemical gold-catalyzed coupling reactions is a challenge. Now, an oxidation relay using aryl radical formed in-situ from hydrazine offers a solution to this problem.

The rapid development of gold redox chemistry over the past decade opens an exciting new direction in catalysis. The high oxidation potential between gold(I) and gold(III) (1.41 V) results in fast Au^{III} reductive elimination, leading to the discovery of new reactivity for C-C coupling reactions. However, to achieve Au^{I} oxidation, strong oxidants, such as selectfluor[1] or PIDA[2], are required, which inevitably causes substrate limitation due to compatibility issues. Photo-[3] or base-promoted[4] diazonium salt oxidation both provide mild conditions to produce L-Au^{III}-Ar intermediates through the formation of an aryl radical. However, the requirement of electron deficient arenes to ensure effective Au^{I} oxidation and the potential side reaction of electrophilic addition to the diazonium salts limits the application of this protocol.

The fast growth of synthetic organic electrochemistry in recent years has led to the first report of anodic oxidation (EAO) gold redox catalysis for terminal alkyne cross-coupling C(sp)-C-(sp)[5], where conditions were developed to replace the undesired reduction of gold cations at the cathode with simple H_2 formation. Later, $C(sp^2)$-$C(sp^2)$ and $C(sp^2)$-C(sp) coupling under EAO conditions were reported using aryl boronic acids and terminal alkynes under basic conditions with oxygen as the sacrificial oxidant, which is reduced at the cathode[6]. In both examples, the key oxidation steps occurred at the in-situ-formed L-Au^{I}-R/Ar intermediate. Because transmetalation is required for the formation of L-Au^{I}-Ar, the "matching" of gold catalyst and substrate becomes critical, making the conditions sensitive for different substituents and gold catalysts (for instance, anode electronic field repulsion toward gold cations). Now, Xie and co-workers report an alternative pathway to obtain the L-Au^{III}-Ar intermediate under EAO conditions through an oxidation relay using aryl hydrazine and a neutral dppm$(AuCl)_2$ catalyst (Fig. 1).[7] Upon electrochemically promoted hydrazine oxidation, the reactive intermediate (likely an aryl radical) is produced and applied as an oxidant for direct Au^{I} oxidation. Using this method, direct C-C coupling can be achieved with excellent functional group tolerability and biocompatibility, providing a new protocol for gold redox catalysis under mild conditions with readily available starting materials.

The authors first optimize the reaction conditions with 2-aminophenylacetylene and 4-cyanophenyl hydrazine. Through the condition screening, the importance of $^{n}Bu_4NOAc$ as electrolyte and a catalytic amount of 1,10-phenanthroline ligands are identified as the critical factors for stabilizing the Au^{III} intermediate. The bis-gold catalyst dppm$(AuCl)_2$ is identified as the optimal catalyst. Control experiments confirm that both gold and current are crucial for the transformation.

Exploration of the substrate scope shows that both aromatic and aliphatic alkynes are suitable, giving the desired C-C coupling in good yields (Fig. 1b). Notably, substrates bearing intramolecular nucleophiles are also tolerated under these conditions, giving neither nucleophile oxidation nor alkyne addition products. These results confirm the orthogonal reactivity of this EAO strategy compared with classical gold chemistry. Regarding the hydrazine substrates, substitution on the aromatic ring has little effect on the yields, highlighting the improved reactivity of this protocol over photo-assisted diazonium salt decomposition gold oxidation methods.

Perhaps the most impressive benefit of this method is the excellent biocompatibility when using functionalized substrates containing “bio-handles”. Biomolecular skeletons, including amino acids, nucleotides and sugar structures could be installed on the alkyne coupling partners and all these biomarkers remained intact upon exposure to the reaction conditions, giving the desired products in moderate to good yields. The addition of excess biomolecules to the standard reaction conditions further testifies to the biocompatibility of these conditions, where similar performance is observed with little effect on the desired reaction. Considering the possibility of rapid N or O coordination with metal catalysts, this excellent tolerability towards biomolecules showcases the unique compatibility of this electrochemical gold redox catalysis process with biomedicinal applications expected in the future.

Mechanistic studies in this work to explore the key factors of this transformation show that TEMPO addition gives the radical trapping products, confirming the oxidation of hydrazine prior to the gold catalyst. The observation of the intramolecular aryl radical trapping product provides further evidence for this process. The linear free-energy relationship (Hammett equation) on aryl hydrazines shows a positive slope, which is consistent with the expected easier gold(I) oxidation with electron deficient arene radicals. Cyclic voltammetric studies provide direct evidence of a lower oxidative potential associated with the aryl hydrazine (0.53 V) than gold(I) [1.06 V for Au(I) to Au(II)]. Based on these results, the oxidation relay mechanism is proposed (Fig. 1c): aryl hydrazine EAO oxidation followed by single electron oxidation on gold(I) to give the key L-Au^{III}-Ar intermediate.

Xie and co-workers introduce a fantastic C(sp^2)-C(sp) coupling approach combining gold redox catalysis with electrochemistry. This strategy achieves the coupling with no need of external oxidants. The biocompatibility of this transformation highlights the synthetic robustness and possible late-stage functionalization for future biomedicinal applications. The mechanistic studies confirm the oxidation relay in this gold redox chemistry, making the hydrazine-gold EAO protocol a promising new strategy for further development in the future.

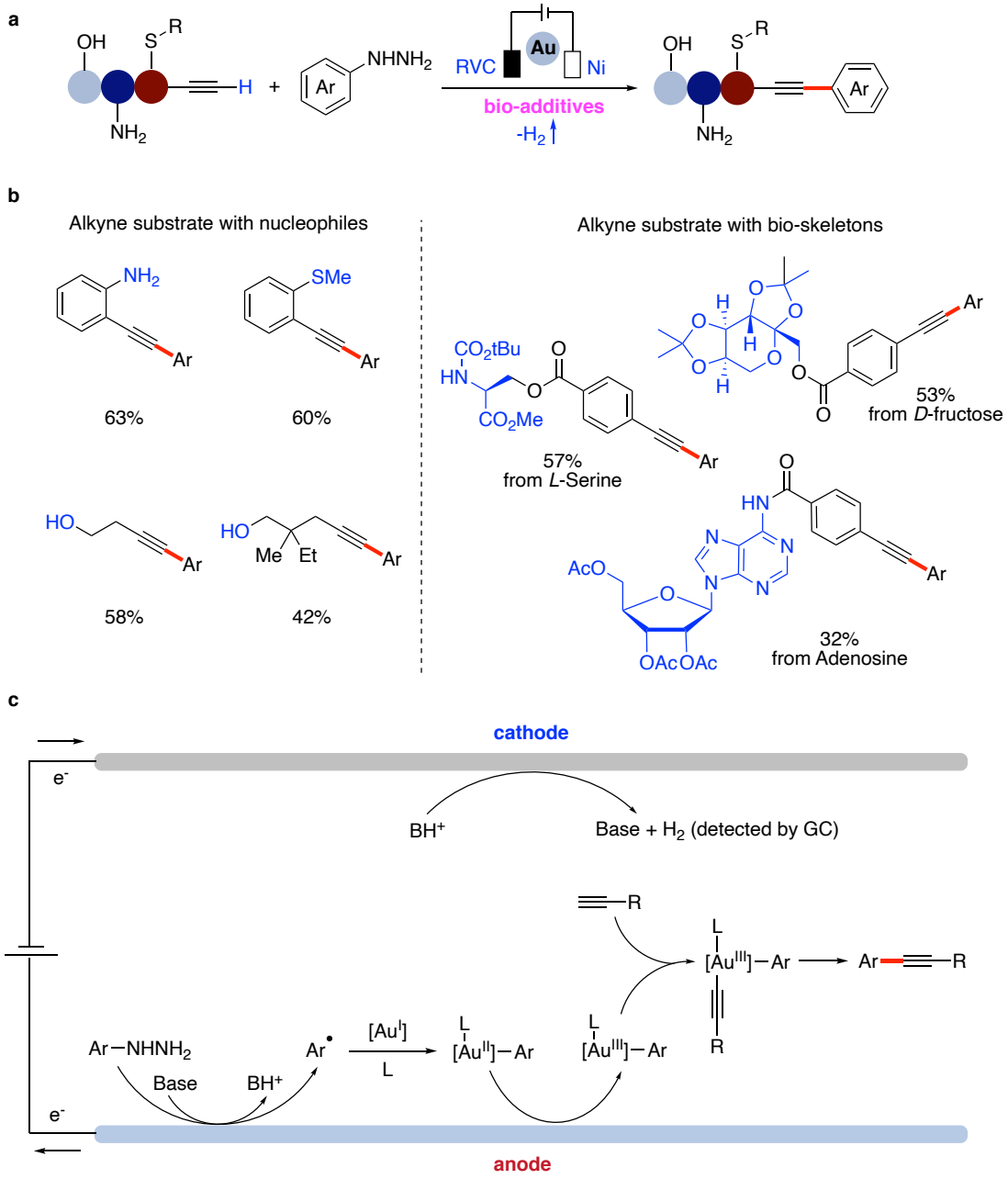

Fig. 1, An overlook of electrochemical gold-catalyzed coupling reaction. a, General reaction performance of EAO gold redox catalysis. **b**, Selected substrates of different alkyne derivatives, including substrates with bio-skeletons attached. **c**, Proposed reaction mechanism. (RVC: reticulated vitreous carbon; GC: gas chromatography; L: Ligand)

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