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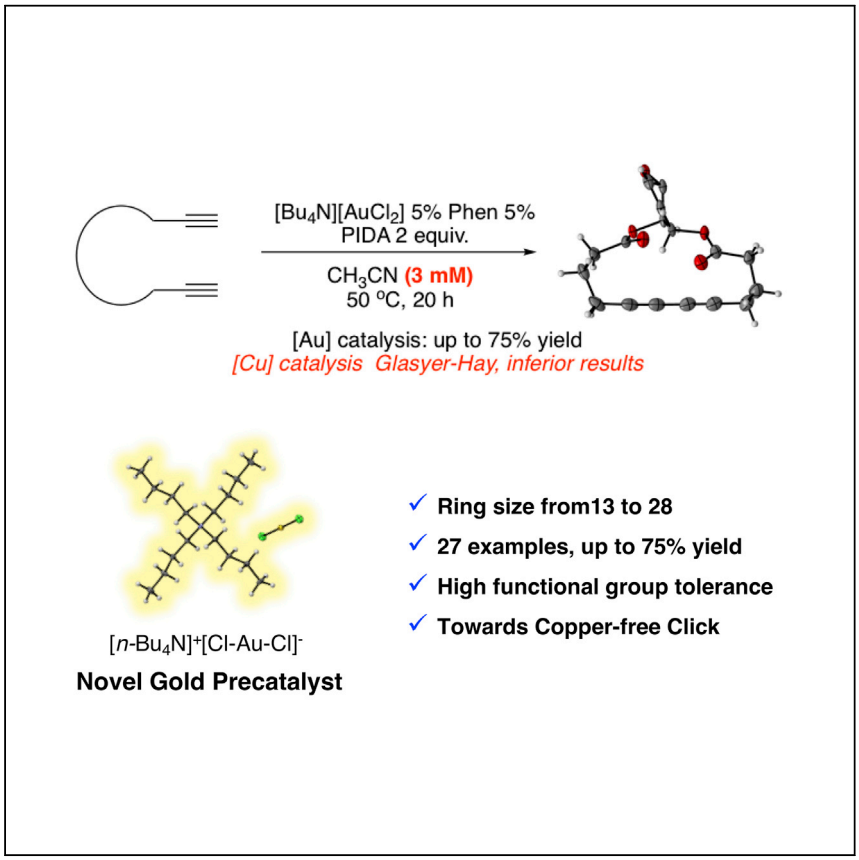
Gold-Catalyzed Oxidative Coupling of Alkynes toward the Synthesis of Cyclic Conjugated Diynes



Gold-catalyzed oxidative coupling of alkynes was developed as an efficient approach for the synthesis of challenging cyclic conjugated diyne. Compared with copper-promoted oxidative coupling, this protocol allowed macrocyclization under dilute conditions with good overall reactivity and high functional group tolerance. The success in achieving copper-free click chemistry on cyclic conjugated diyne highlights its potential application in biological and medicinal research.

Xiaohan Ye, Haihui Peng, Chiyu Wei, Teng Yuan, Lukasz Wojtas, Xiaodong Shi

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HIGHLIGHTS

First synthesis of challenging cyclic conjugated diynes via gold catalysis

$[(n\text{-Bu})_4N]^+[Cl\text{-Au-}Cl]^-$ salt as a pre-catalyst toward gold redox chemistry

Facile access to functionalized cyclic conjugated diynes with 13–28 member rings

Copper-free azide-alkyne cycloaddition for potential biological research

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Gold-Catalyzed Oxidative Coupling of Alkynes toward the Synthesis of Cyclic Conjugated Diynes

Xiaohan Ye,[1] Haihui Peng,[1] Chiyu Wei,[1] Teng Yuan,[1] Lukasz Wojtas,[1] and Xiaodong Shi[1,2,*]

SUMMARY

Gold-catalyzed oxidative coupling of alkynes was developed as an efficient approach for the synthesis of challenging cyclic conjugated diynes (CCD). Compared with the classic copper-promoted oxidative coupling reaction of alkynes, this gold-catalyzed process exhibited a faster reaction rate due to rapid reductive elimination from the Au(III) intermediate. This unique reactivity thus allowed a challenging diyne macrocyclization to take place with high efficiency. Condition screening revealed an $[(n\text{-Bu})_4N]^+[Cl\text{-}Au\text{-}Cl]^-$ salt as the optimal pre-catalyst. Macrocycles with ring size between 13 and 28 atoms were prepared in moderate to good yields, which highlighted the broad substrate scope of this new strategy. Furthermore, the synthetic utilities of the CCDs for copper-free click chemistry have been demonstrated, showcasing the potential application of this strategy in biological systems.

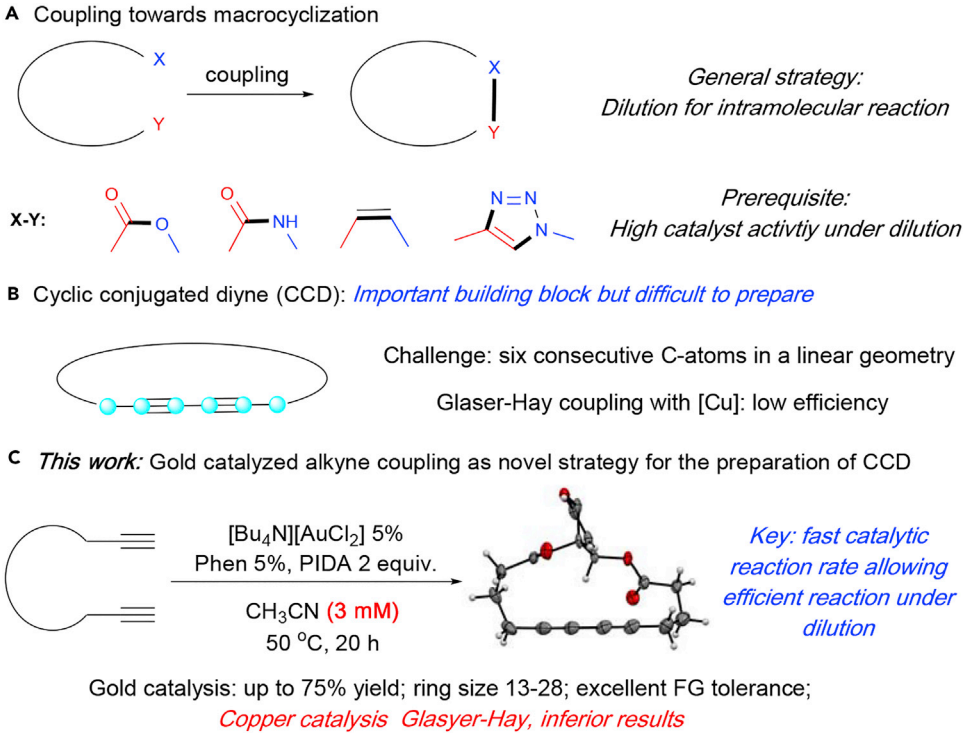
INTRODUCTION

Macrocycles are a group of important and fascinating compounds that exhibit broad utilities in chemical, material, and biological research.[1–5] Successful macrocyclization strategies often rely on the reaction rate differences between intramolecular cyclization and (problematic) intermolecular oligomerization or polymerization.[6–9] Thus, the two general approaches for selective macrocyclization are (1) pre-organization of reactant conformation to favor the cyclization and (2) reduction of the intermolecular reaction rate through significant dilution. One major concern for achieving macrocyclization under highly diluted conditions is the efficiency of the catalyst. Some representative macrocyclization strategies are shown in Scheme 1A, including Nozaki-Hiyama-Kishi macrocyclization,[10–14] ring-closing metathesis,[15–18] and intramolecular alkyne-azide cycloaddition (CuAAc).[19–22]

The intrinsic reactivity of C≡C triple bonds allows alkynes to occupy a privileged position in organic synthesis. Among alkyne derivatives, conjugated diynes have shown interesting properties in chemical, medicinal, and material research.[23–27] A typical conjugated diyne is unique in that six consecutive atoms are arranged in a linear geometry (Scheme 1B). Thus, macrocycles containing conjugated diynes must possess a flexible backbone and fairly large ring size to minimize the strong ring strain. A significant breakthrough in cyclic conjugated diynes (CCD) synthesis was the recent work reported by Collins and coworkers using a phase-transfer system.[28–30] In their work, a mixture of MeOH and PEG_{400} (1:2) was used to generate a heterogeneous biphasic reaction environment. Although the exact mechanism remains uncertain, they proposed that the biphase environment allowed the formation of a metal-acetylide at the solvent interface and prevented

The Bigger Picture

Macrocycles are important structural moieties in medicinal and biological research, and efficient methods for macrocyclization are always in high demand. With the unique conformation having six carbon atoms in a linear geometry, the cyclic conjugated diynes (CCD) present greater synthetic challenges and have been much less explored. Therefore, application of these unique macrocycles in biological studies is largely unexplored. Here, we describe the discovery of gold-catalyzed Glaser-Hay type oxidative coupling of terminal alkynes to achieve CCD under diluted conditions with broad substrate scope and great functional group compatibility. Taking advantage of the 14-member cyclic diyne, a copper-free click chemistry was achieved, which provided an effective alternative strategy for the traditional cyclooctyne-based azide-alkyne cycloaddition, suggesting a promising future for this method in tackling challenging problems in related biological and medicinal research.



Scheme 1. Challenges in the Synthesis of Cyclic Conjugated Diyne

intermolecular polymerization. This seminal work was the best condition reported so far for the practical synthesis of CCDs with flexible linkers. One major concern about that method was that the biphase system required very complex conditions for optimal performance (25%–100% $CuCl_2$, 25%–100% $Ni(NO_3)_2$ $6H_2O$, 3 equiv Et_3N, 5 equiv pyridine, 60°C, O_2, 1–2 days), and some substrates (such as phenol ester, see below) are not tolerated under these conditions. Thus, novel approaches for this extremely challenging transformation are highly desirable, especially with a complementary substrate scope and better functional group tolerability.[31–35] In this work, we report gold-catalyzed oxidative coupling of terminal alkynes as an alternative approach to construct CCDs. The key to this success was the realization of a faster C_{sp}-C_{sp} reductive elimination on gold(III) complexes (comparing with copper-catalyzed Glaser-Hay conditions),[36] which allowed more efficient alkyne coupling at low concentration. Cyclic diynes of between 13 and 28 atoms were prepared in moderate to good yields; copper catalysts provided inferior results due to the slow reaction rate under diluted conditions (Scheme 1C).

RESULTS AND DISCUSSION

Our interest in developing new strategies for the synthesis of CCDs was initiated from our recent success in gold-catalyzed cross-coupling of terminal alkynes.[37] In that study, we discovered that oxidative coupling of terminal alkynes could be achieved using a gold catalyst under suitable conditions (Phen as ligand and bisacetoxyiodobenzene [PIDA] as oxidant). Compared with the copper-promoted Glaser-Hay conditions,[38–41] gold catalysts gave excellent cross-coupling selectivity between aromatic alkynes and aliphatic alkynes. Besides the excellent selectivity, we also observed a much faster reaction rate with gold-catalyzed conditions over copper.[42–45] To further validate this key observation, we conducted a kinetic study under three different conditions as shown in Figure 1.

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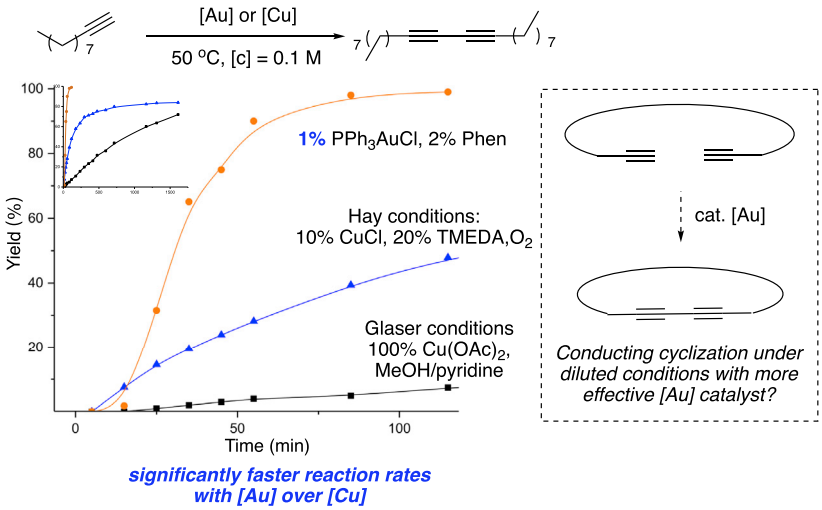


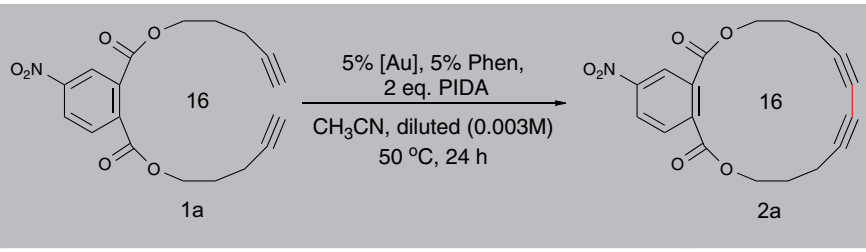
Figure 1. Significantly Faster Reaction Rate of Gold-Catalyzed Coupling
The reaction conditions are detailed in the Supplemental Information.

Under identical reaction temperature and concentration (50°C, 0.1 M), 1% PPh_3AuCl gave a significantly faster reaction rate ($t_{1/2}$ = 45 min) than either Hay or Glaser conditions, which required a much higher catalyst loading (20% or 100%). Encouraged by this result, we explored the cyclization of terminal alkyne **1a** (Table 1). Interestingly, under previously reported optimal conditions (5% PPh_3AuCl, 10% Phen, and 2 equiv PIDA), the desired cyclization product **2a** (ring size = 16) was obtained in less than 10% yield, although complete consumption of **1a** was achieved within 12 hr even at very low concentration with [c] = 0.003 M (entry 1). Slow addition of **1a** over time (24 hr) with a syringe pump improved the yield only slightly to 12% (entry 2). In both cases, the complete conversion of alkyne **1a** indicated the gold catalyst could successfully promote alkyne oxidative coupling even at low concentration. However, polymerization product was obtained as the dominant side product. These results clearly illustrated the great challenge associated with this macrocyclization. To further optimize this reaction, we screened various gold catalysts. The results are summarized in Table 1.

To improve the selectivity toward desired intramolecular cyclization over intermolecular polymerization, we wondered whether bis-gold complexes could improve the reaction performance through a faster transmetalation between two gold atoms in one catalyst.[46] Several bis-gold catalysts were tested. Interestingly, whereas dppm, dppp, and BINAP-bound gold complexes gave poor results similar to PPh_3AuCl (entry 3), a slightly improved yield (15%) of **2a** was obtained using Xantphos$[AuCl]_2$ **cat-1** (entry 4). Surprisingly, simply switching the catalyst to *t*-BuXantphos$[AuCl]_2$ **cat-2**, CCD **2a** was obtained in 75% isolated yield (entry 4), significantly higher than previous cases. It was not clear to us why these two catalysts showed such a dramatic difference until we successfully obtained the crystal structures of both catalysts as shown in Figure 2.

For Xantphos-Au complex **cat-1**, a Au–Au distance of 2.962 Å was observed in L-Au-Cl complex. Interestingly, for *t*-BuXantphos, L-Au-Cl type complex was not formed as revealed by X-ray. Instead, the complex is a salt with $[t\text{-BuXantphosAu}]^+$ as cation and $[Cl\text{-Au-Cl}]^-$ as anion. The P-Au-P complex was formed presumably due to the strong

Table 1. Optimal Condition Screening



Entry	Reaction Conditions[a,b]	1a Conversion (%)	2a (%)
1	5% PPh_3AuCl, 5% Phen, 2 equiv PIDA, 50°C	100	<10
2	Entry 1, syringe pump addition of **1a**	100	12
3	$L[AuCl]_2$ (10%): L = dppm, dppp, BINAP	100	<10
4	10% Xantphos[Au_2Cl_2], **cat-1**	100	15
5	10% *t*-BuXantphos[Au_2Cl_2], **cat-2**	100	75
6	Entry 1, [Au] = 5% [*t*-BuXantphosAu]$^+$[BF_4]$^-$, **cat-3**	<5	ND
7	Entry 1, [Au] = 5% [(*n*-Bu)$_4$N]$^+$[Cl-Au-Cl]$^-$, **cat-4**	100	75
8	entry 7 without PIDA	<5	ND
9	entry 7 without Phen	<5	ND
10	Glaser conditions: 100% $Cu(OAc)_2$, MeOH/pyridine, 50°C, 24 hr	50	12
11	Hay conditions: 20% CuCl, 40% TMEDA, *i*PrOH, O_2, 50°C, 24 hr	20	<10
12	Collins' biphase conditions	100	60
13	other metal catalysts: Rh, Ag, Pt, Ru, Fe, Ni, Pd	<25	<5

[a]Reaction conditions: 5 mol% catalyst and 5% Phen was added to a MeCN solution (30 mL) of 1a (0.1 mmol) and PIDA (0.2 mmol), and reaction was kept under Ar at 50°C for 24 hr.

[b]Conversion and yield were determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

steric hinderance caused by the *t*-Bu group.[47–49] Clearly, the outstanding catalytic activity of the gold catalyst **cat-2** toward cyclic diyne formation must be associated with its unique structure. This discovery is crucial because it revealed a potential new type of gold catalyst (other than L-Au-Cl) that might provide superior reactivity and efficiency toward the preparation of challenging CCDs. The question is which one of the two species in **cat-2**, [P-Au-P]$^+$ or [Cl-Au-Cl]$^-$ (or both), is the key component for the observed excellent reactivity. To explore this crucial mechanistic question, we prepared two gold complexes: [*t*-BuXantphosAu]$^+$[BF_4]$^-$ (**cat-3**) and [(*n*-Bu)$_4$N]$^+$[Cl-Au-Cl]$^-$ (**cat-4**). Both complexes are characterized by X-ray (Figure 2). Under identical conditions, [*t*-BuXantphosAu]$^+$[BF_4]$^-$ (**cat-3**) gave almost no reaction (entry 6). In contrast, a high yield of cyclization product **2a** was obtained using [(*n*-Bu)$_4$N]$^+$[Cl-Au-Cl]$^-$ (**cat-4**) as the catalyst (entry 7). The active gold species in the catalytic cycle is still unclear at this moment; it is likely that **cat-4** only serves as a pre-catalyst, which is oxidized by PIDA to form a Au(III) salt or complex that is the real catalyst in this system. These results not only confirmed that [Cl-Au-Cl]$^-$ was a superior pre-catalyst for alkyne macrocyclization over traditional L-Au-Cl catalyst, but also suggested [(*n*-Bu)$_4$N]$^+$[Cl-Au-Cl]$^-$ (**cat-4**) as the optimal pre-catalyst (cheaper and more efficient) for the challenging CCD synthesis. Although [(*n*-Bu)$_4$N]$^+$[Cl-Au-Cl]$^-$ salt has been known since 1973 and is commercially available (CAS 50480-99-4),[50] this is the first time that the catalytic reactivity of [(*n*-Bu)$_4$N]$^+$[Cl-Au-Cl]$^-$ salt has been unveiled as a pre-catalyst toward gold redox chemistry. Furthermore, Phen ligand is crucial to stabilize the Au(III) intermediate and presumably has a significant influence on the rate of reductive elimination as suggested in our previous work (entry 9).[37] Notably, under typical copper-promoted Glaser or Hay conditions, less

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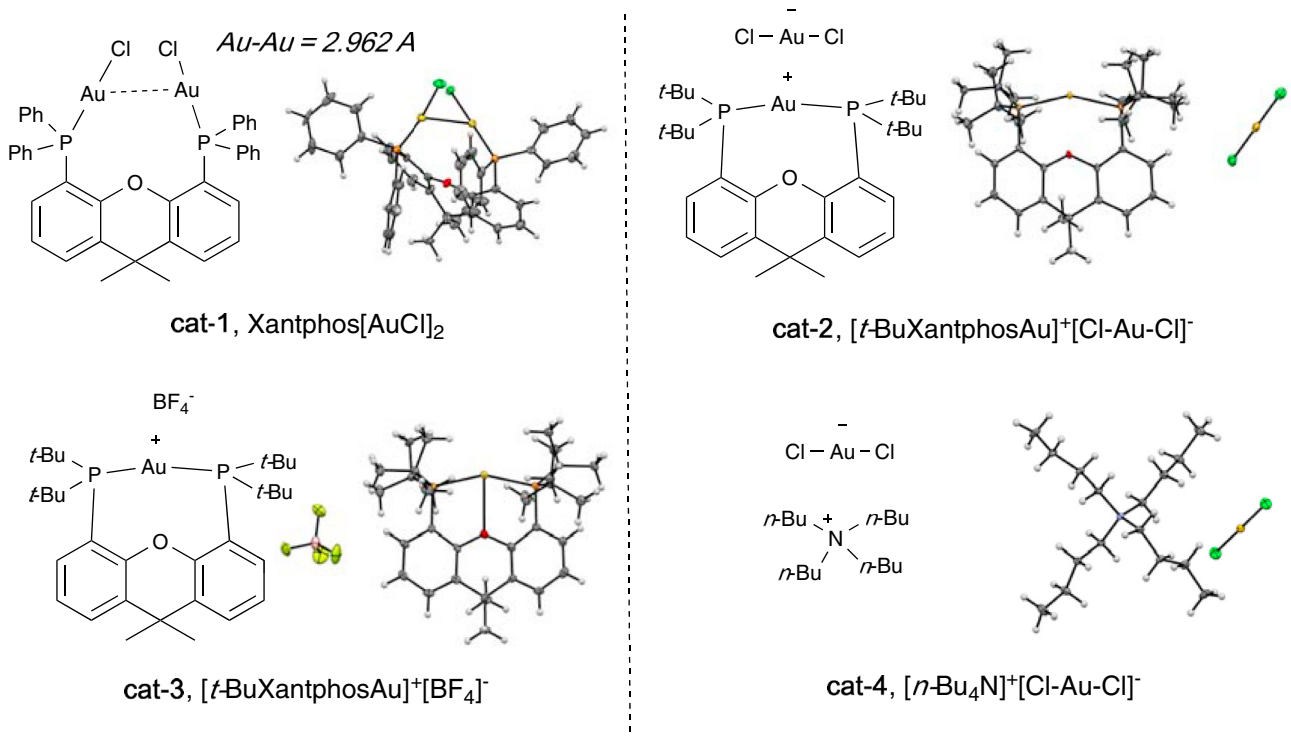


Figure 2. X-Ray Crystal Structures of "Xantphos-Au" Complexes
The method for catalyst synthesis is detailed in the Supplemental Information.

than 15% yield of product was obtained with low conversion. Under the biphase conditions reported by Collins' group, a lower yield was obtained. All other metal catalysts tested (Rh, Ag, Pt, Ru, Fe, Ni, Pd) failed to promote this transformation, which highlighted the unique reactivity of this $[Cl\text{-}Au\text{-}Cl]^-$ type of pre-catalyst for CCD synthesis. With the optimal conditions revealed, we explored the scope of this macrocyclization method. The results are summarized in Figure 3.

First, diynes containing different lengths of alkyl linkers to a 4-nitrophthalic ester backbone (**2a**-**2f**) were synthesized and subjected to the optimized reaction conditions. To our delight, macrocycles with ring size ranging from 14 to 28 were obtained in moderate to good yields. Gram-scale synthesis of **2a** was also successfully performed without dramatic erosion in product yield. Notably, despite significantly increased ring strain, a 14-member ring could be effectively achieved with modest yield, which is remarkable for CCD synthesis. Attempts to form a 12-member ring gave mainly dimerization products along with polymerization. When the targeted ring size reached 28, the yield of desired products decreased due to the increased polymerization by-products. Next, substrates with different backbones were investigated. Substrates with flexible aliphatic backbone were suitable for this reaction, providing desired products in moderate yields (**2g**, **2h**). Other aromatic esters such as phthalic ester (**2i**) and naphthalic ester (**2j**) also afforded desired products in good yields. Remarkably, substrate with an alkene backbone (**2i**) was also successful, with no decomposition of the product observed under the oxidative conditions. Substrate containing an alkyne backbone (**2t**) was also tolerated for this reaction with no hydration product observed. Both aryl alkynes (**2o**) and benzyl alkynes (**2r**) were suitable. Alkynes with a labile benzoyl group at the propargyl and homopropargyl position (**2u** and **2v**) also proved successful. The D-Glucal derivative **2n** and Camphor

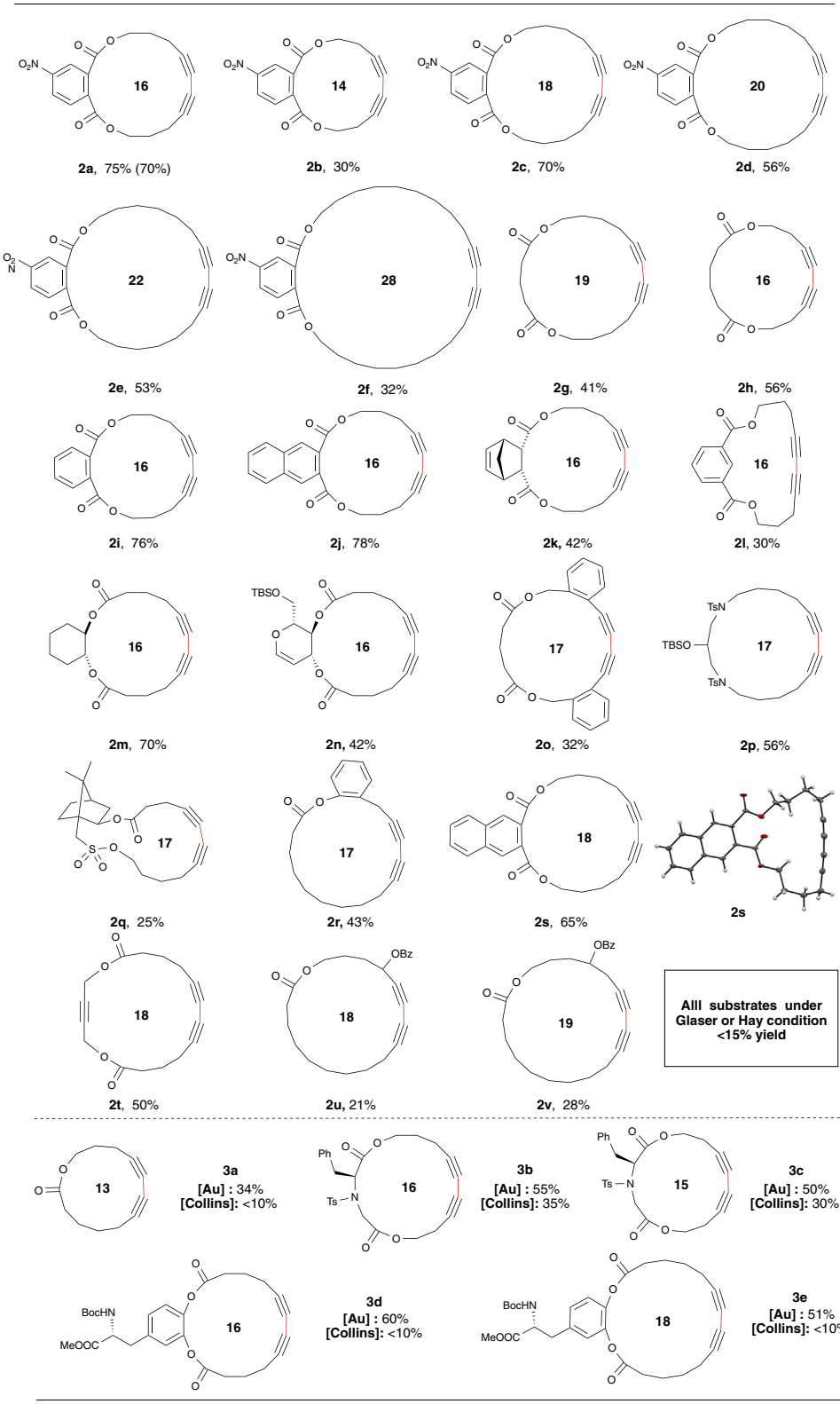


Figure 3. Substrate Scope for Macrocyclization

Reaction conditions: All the yields are isolated yield. 5% catalyst and 5% Phen were added to a MeCN solution (30 mL) of 0.1 mmol substrates and PIDA (0.2 mmol), and reaction was kept under Ar at 50°C for 24 hr. Isolated yield. 0.5 mmol scale.

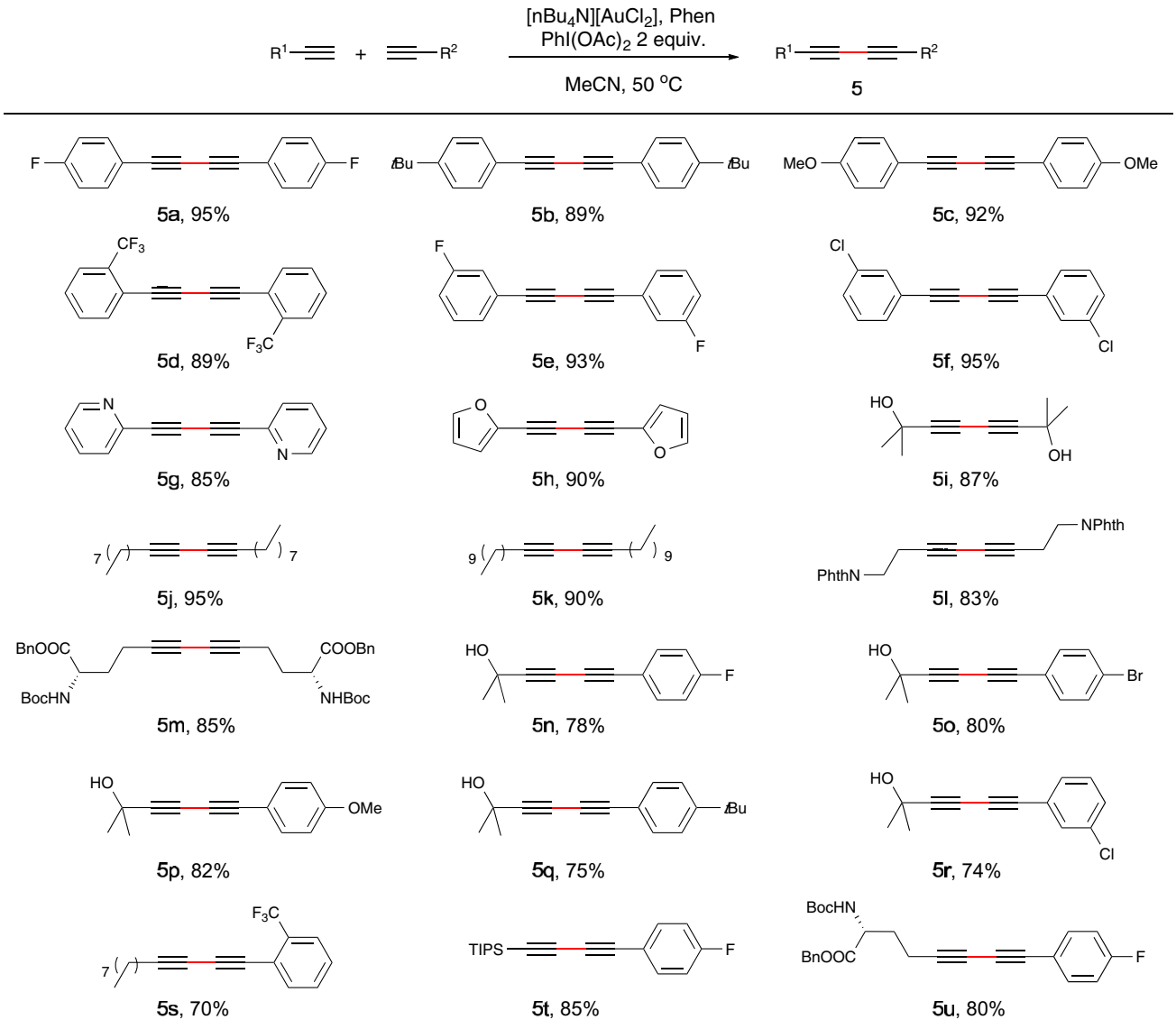
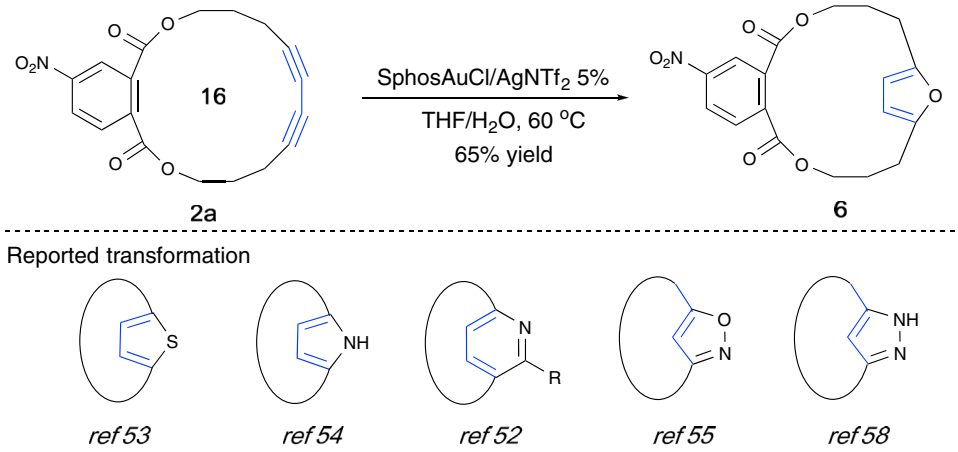


Figure 4. Substrate Scope for Intermolecular Homo-/Cross-Coupling

Reaction conditions for homo-coupling: 1% catalyst and 2% Phen were added to a MeCN solution (5 mL) of alkyne (1 mmol) and PIDA (1 mmol), and the reaction was run at 50°C. Reaction conditions for cross-coupling: 5 mol% catalyst and 10% Phen were added to a MeCN solution (800 μL) of aryl alkyne (0.2 mmol), aliphatic alkyne (0.6 mmol), and PIDA (0.4 mmol), and the reaction was run at 50°C. Isolated yield.

derivative **2q** were successfully prepared, further demonstrating the exceptional functional group tolerability of this gold catalytic method. The structures of the conjugated dienes were confirmed by the X-ray crystal structure of **2s** and **2n**. Although Collins' phase-transfer method is a benchmark standard for CCD synthesis, one limitation of Collins' method was the requirement of a hydrophobic flexible chain to adopt the biphase conditions. As a result, it is ineffective toward a strained 13-member ring with short alkyne chain (**3a**). Also, some challenge substrates containing polar amino acid backbones such as **3b–3e** gave very low yields. Remarkably, the gold-catalyzed conditions provided significantly better results for these substrates, forming the desired CCD products in moderate yields. In all cases, Glaser or Hay conditions provided desired macrocyclization in less than 15% yield. Overall,



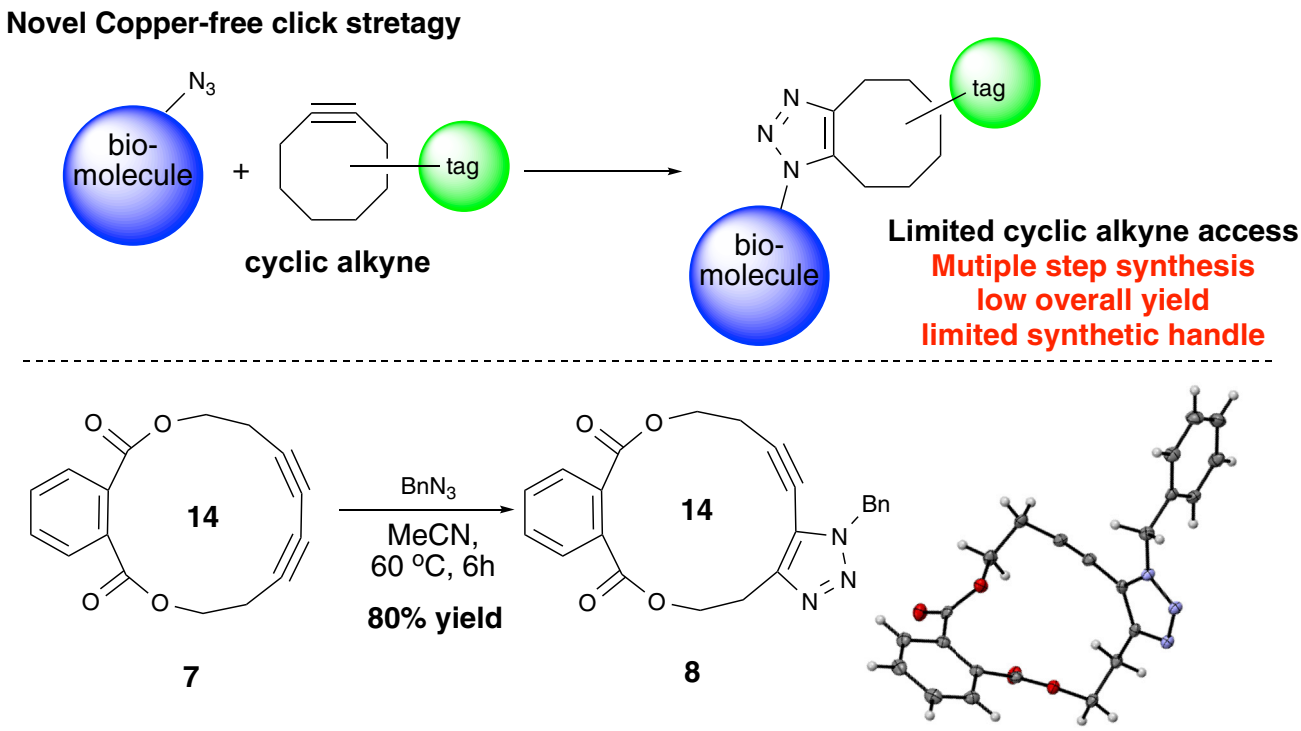
Scheme 2. Synthesis of Heterocycles from Cyclic Conjugated Diyne

all these results clearly demonstrated the great potential of this new method for CCD synthesis, especially as a complementary approach for the previously reported state-of-the-art Collins' method.

After the successful realization of this gold-catalyzed oxidative macrocyclization, we envisioned that this protocol could also be used in intermolecular alkyne coupling. As demonstrated in Figure 4, homo-coupling of various aromatic and aliphatic alkynes was achieved in excellent yields. Unlike Corma's condition using Selectfluor as oxidant,[42,51] this method successfully promoted the homo-coupling of aliphatic alkynes with long chains (**5j**, **5k**) in excellent yield. Various functional groups were tolerated, such as pyridine (**5g**), thiophene (**5h**), propargyl alcohol (**5i**), and even amino acid (**5m**). Cross-coupling between aryl and aliphatic alkynes was also explored. When the ratio of aryl and aliphatic is 1:3, the selectivity of cross- versus homo-coupling can reach 7:1 (**5n**), with 78% isolated yield of cross-coupling product. Similar selectivity and yield was observed for cross-coupling between different aromatic and aliphatic alkynes. Although this result is not superior compared with our previously reported dppm$(AuBr)_2$ system, it offered an alternative option with cheap and readily available $[(n\text{-}Bu)_4N]^+[Cl\text{-}Au\text{-}Cl]^-$ salt. Overall, we demonstrated the capability of $[(n\text{-}Bu)_4N]^+[Cl\text{-}Au\text{-}Cl]^-$ salt in promoting intermolecular alkyne coupling.

Furthermore, the resulting CCDs are valuable synthons that can be easily converted into other useful compounds. The transformation of diynes into furan **6** was carried out under simple gold-catalyzed conditions as shown in Scheme 2. Conversions to other heterocycles, such as thiophene and pyridine, can be readily achieved based on similar known methods.[52–58]

One very important application of cycloalkyne is copper-free azide-alkyne cycloaddition, which has received tremendous attention in recent years as a bio-compatible labeling strategy under mild conditions.[59–65] The success of this strategy relies on the ring strain of the cycloalkyne. Currently, difluoro-modified cyclooctynes are used as the benchmark cycloalkynes for the metal-free click reaction. However, the preparation of these compounds was not straightforward (multiple steps with overall low yields) and often with poor functional group diversity. Therefore, a new strategy for metal-free click chemistry is highly desirable. With easy access to mid-size cyclic diynes, we postulated that the CCDs could be another type of coupling partner toward azides, achieving metal-free click chemistry under mild conditions. We envisioned the



Scheme 3. Metal-Free Click Chemistry Using Cyclic Conjugated Diyne

14-membered cyclic diynes could be ideal for this purpose with good stability and enough ring strain. To test our hypothesis, we prepared cyclic diyne **7** and charged it with BnN_3 in MeCN. The desired triazole **8** was obtained in good yield (80% at 60°C). Notably, a single regio-isomer was obtained and its structure was unambiguously confirmed by X-ray crystallography (Scheme 3). To the best of our knowledge, this is the first example to achieve copper-free cycloaddition with a CCD. Our group is currently evaluating this new methods with regard to CCD ring size, functional group tolerability, and optimal conditions. Those results will be reported in due course. The success of CCD click chemistry highlights the potential application of this gold-catalyzed macrocyclization method in biological and material research.

In summary, for the first time, we report on the challenging synthesis of CCDs under gold-catalyzed macrocyclization conditions. Gold catalyst $[(n\text{-}Bu)_4N]^+[Cl\text{-}Au\text{-}Cl]^-$ was developed to promote this transformation with broad substrate scope and excellent functional group tolerance. This method is straightforward and efficient and represents a complementary strategy compared with current state-of-the-art methods. Synthetic utility of cyclic diynes was demonstrated by converting them to various heterocycles. The facile copper-free azide-alkyne cyclization with 14-member CCDs further emphasizes the promising future of this new methodology in biological and material research.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

DATA AND SOFTWARE AVAILABILITY

The structure of **cat1**-**cat4**, **2n**, **2s**, and **8** reported in this article has been deposited in the Cambridge Crystallographic Data Centre. The accession numbers for reported

compounds in this paper are CCDC: 1821105, 1821106, 1821107, 1821101, 1821103, 1821102, and 1821104, correspondingly.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, 177 figures, 7 tables, and 7 data files and can be found with this article online at https://doi.org/10.1016/j.chempr.2018.07.004.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

X.Y. discovered the reaction. X.Y. performed the optimization. X.Y., H.P., C.W., and T.Y. investigated the scope of the substrate and performed the application. L.W. carried out the X-ray crystallography analysis. X.S. directed the project and wrote the manuscript with input from all authors. All authors analyzed the results and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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