Ligand-Assisted Gold-Catalyzed Efficient Alkynylative Cyclization with Terminal Alkynes Using H_2O_2 as Oxidant

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ABSTRACT: The gold-catalyzed cyclization-functionalization is a powerful approach to construct high-value organic molecules. However, current strategies mainly rely on expensive external oxidants or pre-functionalized substrates, which exhibit low atom economy and high costs. Considering the current increasing demand for environmentally friendly and atomically efficient processes, the development of greener and more efficient synthetic strategies becomes more valuable and attractive. To circumvent these drawbacks, we developed a green gold-catalyzed cyclization-functionalization strategy using hydrogen peroxide as oxidant. A direct construction of 3-alkynylbenzofurans from terminal alkynes was possible by this gold-catalyzed process. Green and inexpensive oxidants, simple gold catalysts, mild reaction conditions, high atom economy, remarkable selectivity, wide substrate scope, broad functional group compatibility and a facile gram-scale synthesis make this alkynylative cyclization method practical for many forms of cyclization reactions. In contrast to prior methods neither pre-functionalized alkynes nor expensive external oxidants are needed.

As a powerful method for the preparation of complex organic molecules, homogeneous gold catalysis has received extensive attention for its strong ability to activate C-C double or triple bonds, especially for the selective and efficient promotion of different cyclization reactions.[1-4] Typically, *in situ* protodeauration of organogold intermediates terminates the catalytic cycle to afford hydrogen-functionalized products.[1,2] In recent years, more attention has been devoted to the *in situ* post-functionalization of gold intermediates instead of simple protodemetallation.[3,4] Gold-catalyzed cross-coupling reactions with strong external oxidants, such as hypervalent iodine reagents or F^+ donors have shown to be effective for the *in situ* functionalization to construct complex organic molecules.[4] However, these reagents are often costly and show low atom economy. To avoid the burden of such waste-generating oxidants, a Au/Pd dual catalytic system proved to be effective for the cyclization-functionalization process, however the very low number of reports suggest that its general application remains challenging.[5,6] In addition, the use of special pre-functionalized substrates such as aryldiazonium salts,[7-11] alkynyl hypervalent iodine reagents,[12-16] alkynyl halides,[17-19] *etc.* also gave access to Au^I/Au^{III} catalytic cycles without external oxidants to afford cyclic functionalized molecules. Although the use of external oxidants is avoided, its limitations are also significant, such as air sensitivity, the need for expensive photosensitizers and special photoreactors.[7-11,17,19] Furthermore, the synthesis of the applied reagents is not straightforward,[12-16] resulting in low atom economy and high costs.

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Since Trost first proposed the concept of atom economy in 1991,[20] ways to improve the atom-efficiency of chemical reactions have become one of the main issues in all fields of synthetic chemistry, and the increasing demand for environmentally benign and atom efficient processes has led to a growing interest on the invention of greener and more efficient synthetic strategies.[21,22] While commonly used stoichiometric oxidants, such as perchlorate, permanganate, hypervalent iodine reagents or F^+ donors among others generate large amounts of waste, H_2O_2 can serve as an environmentally friendly and inexpensive oxidant, with H_2O being the only by-product. In addition, high atom economy can be achieved and costs are low. As a consequence of its high oxidation potential (+1.78 V),[23] combined with the environmentally friendly properties, H_2O_2 is rapidly replacing commonly used stoichiometric oxidants.[24,25] Based on its redox potential, H_2O_2 can theoretically enable the conversion of Au^I to Au^{III} with an oxidation potential of +1.40 V.[26] However, so far no homogeneous gold-catalyzed oxidative couplings using hydrogen peroxide as an oxidant are found in the literature.[27]

The biggest challenge for a homogeneous oxidative gold catalysis cycle with H_2O_2 as the oxidant is to achieve the oxidation of Au^I to Au^{III} (Fig. 1b). Russell's group demonstrated that Ph_3P as a ligand easily dissociates from Au^{III} complexes followed by rapid oxidation to form Ph_3PO.[28] However, our initial study showed that Ph_3PAuCl was very stable in a 5 M solution of H_2O_2 in MeCN (see Fig. S1 for more details). At first sight, it seems that the linear coordination sphere of Au^I thermodynamically disfavors a coordination of hydrogen peroxide, making it difficult to form the corresponding Au^{III} complex. It is acknowledged that linear two-coordinated Au^I complexes are extremely stable, which are not keen on higher coordination numbers and disfavor oxidative addition.[29] Bourissou's group demonstrated that the reactivity of Au^I complexes can be effectively enhanced by changing the linear state of the Au^I center, hence hemivalent chelating ligands at the Au^I centre were key to trigger oxidative additions.[30,31] Furthermore, Russell's and our group discovered that bidentate *N*-ligands, such as bipyridine (bpy) and 1,10-phenanthroline (phen), which enhance π back-donation from Au^I, boost the oxidative addition progress.[32,33] Considering the above factors and based on our previous research results,[12,13,33] we explored the possibility of the bidentate ligand phen to promote the oxidation of Ph_3PAuCl (see Supplementary Fig. S1 for full details). The results showed that phen can effectively promote the oxidation of Au^I to Au^{III}. Thus, we expect that a strategy for phen-assisted oxidative gold catalysis with H_2O_2 could be achievable. As a test system for a gold-catalyzed cyclization-functionalization reaction with H_2O_2 we selected alkynylative cyclization processes. 2-(Alkynyl)phenols as good cyclization coupling partners, can efficiently provide benzofuran building blocks.[14,17,34] Surprisingly, gold-catalyzed alkynylative cyclization to provide 3-alkynylbenzofurans, based on 2-(alkynyl)phenols and terminal alkynes as coupling partners have no precedent in the literature. Indeed no product was detected if commonly used oxidants, such as $PhI(OAc)_2$ (PIDA) or Selectfluor,[4,35] were applied. Herein, we describe a new ligand-assisted gold-catalyzed alkynylative cyclization with H_2O_2 as an external oxidant, to furnish 3-alkynylbenzofurans from 2-(alkynyl)phenols and terminal alkynes (Fig. 1c).

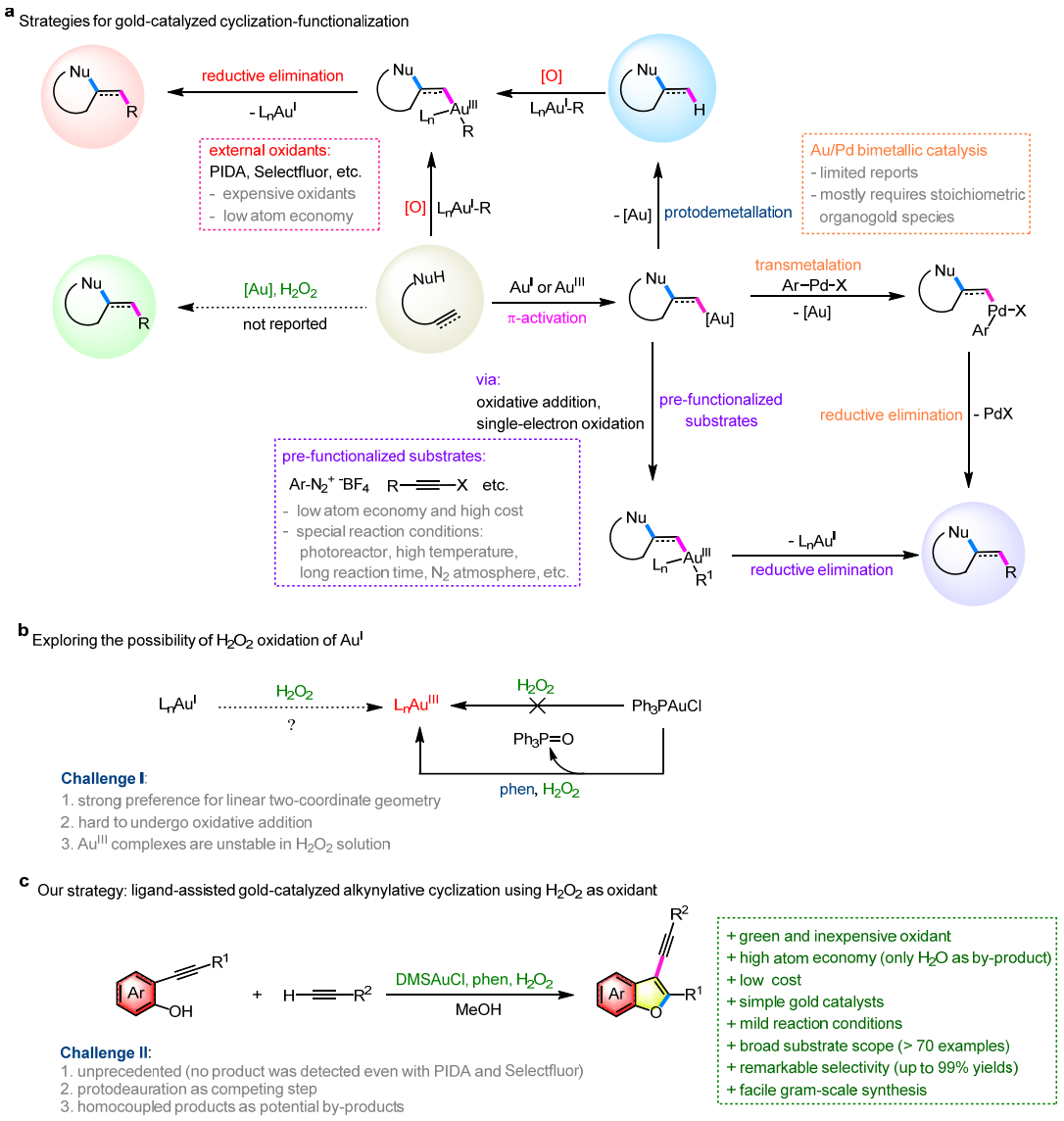


Fig. 1| Gold-catalyzed cyclization-functionalizations. a, Strategies for gold-catalyzed cyclization-functionalization. **b,** Exploring the possibility of the oxidation of Au^{I} by H_2O_2. **c,** Our strategy: Ligand-assisted gold-catalyzed alkynylative cyclization using H_2O_2 as oxidant.

Results

Reaction development. We started our investigation on the gold-catalyzed alkynylative cyclization by using 2-(phenylethynyl)phenol **1a** and 1-ethynyl-4-fluorobenzene **2a** as test system (see Supplementary Tables S1-S6 for full details). We first focused on the investigation of the effect of different ligands on the reaction (Table S1). The bidentate ligand phen turned out to be optimal, furnishing the alkynylative cyclization product **3a** in 99 % yield. Next, we focused on the investigation of the effect of different gold catalysts on the reaction (Table S2). Both mononuclear and binuclear gold complexes delivered the alkynylative cyclization product **3a** in good to excellent yields (76-99%). Other mononuclear gold(I) complexes with significant steric bulk, such as CyJohnPhosAuCl,

gave the product in only low to moderate yields (3-42%). In addition, other reaction parameters were screened including reaction time, equivalents of alkyne **2a**, oxidants, combined equivalents of DMSAuCl, phen and H_2O_2, reaction solvent and reaction temperature (see Supplementary Tables S3-S6 for full details). Considering the comprehensive efficiency, the optimal catalytic system consists of 2.5 mol% DMSAuCl, 10 mol% phen, and 8.0 equivalents of H_2O_2.

Evaluation of substrate scope. With the optimized conditions in hand, we explored the scope of different terminal alkynes **2** to form 3-alkynylbenzofurans **3**, using 2-alkynylphenols **1** as the alkynylative cyclization partners. As shown in Fig. 2A, we first focused on alkynylative cyclization with aromatic terminal alkynes. Aryl alkynes bearing electron-withdrawing groups, such as -F, -Cl, -Br, -I, $-CF_3$, -CN, $-NO_2$, were tolerated well, furnishing the alkynylbenzofurans in yields ranging from 77% to 99% (**3a**-**3g**). A variety of electron-rich aryl alkynes, with electron-donating groups such as -Me, -Et, -^{i}Pr, -^{t}Bu, -OMe, -NHAc, reacted smoothly as well, affording the target alkynylative cyclization products in very good to excellent yields (**3h**-**3n**, 84-97%). It is worth pointing out that the bulky arylacetylenes **2d** and **2l**, and even the more sterically hindered 1-ethynyl-2-isopropylbenzene **2j**, still reacted well, forming the corresponding products (**3d**, **3l** and **3j**) in excellent yields (91-94%). The above results show that the electronic properties and the position of the substituents on the aromatic ring of the terminal arylalkynes have no significant effect on this reaction. Phenylacetylene and naphthylacetylene without substitution at the aromatic moiety proved to be also suitable substrates, providing **3o** and **3p** in 99% and 97% yields, respectively. As expected, heteroaromatic alkynes, including both electron-poor pyridine and electron-rich thiophene substituents, reacted very smoothly as well, affording the corresponding alkynylbenzofurans in excellent yields (**3q**, 95%, **3r**, 99%). Surprisingly, enediynes were tolerated well by the catalytic system to afford alkynylbenzofuran **3s** in 61% yield. In addition, as shown in Fig. 2B, great functional group tolerance was also observed with aliphatic alkynes. Alkylalkynes bearing isobutyl (**3t**), cyclohexyl (**3u**), functional groups such as alcohols (**3v, 3w**), ether (**3x**), cyano (**3y**), chloro (**3z**), phthalimide (**3aa**), ester (**3ab**), amide (**3ac**) and TIPS (**3ad**) were all tolerated in this reaction, leading to the target products in good to excellent yields (63-99%). To underline the synthetic utility of the method, we next evaluated the potential to use this methodology for the introduction of benzofuran units into natural products and synthetic drugs (Fig. 2C). This gold-catalyzed alkynylative cyclization worked well with the substrate **2ae**, derived from Oestron (a weak estrogen), delivering the alkynylative cyclization product **3ae** in decent yield. **2af** and **2ag** as derivatives of small molecule hypolipidemic drugs Gemfibrozil and Fenofibric acid, were amenable to this reaction forming **3af** and **3ag** in 91% and 60% yields, respectively. The derivative **2ah** of Indomethacin, a common non-steroidal anti-inflammatory drug, was also successfully employed to form **3ah** in 68% yield. *L*-Tyrosine derivative **2ai** reacted smoothly as well, to afford alkynylbenzofuran **3ai** in good yield.

Encouraged by these results, the scope for a range of 2-alkynylphenols was further explored (Fig. 2D). First, we varied the R^2 groups of the 2-alkynylphenol partners, both aryl- and alkyl- groups performed efficiently. The electronic properties of the aryl substituents (R^2 groups) had only little influence, electron-donating groups such as Me-,

MeO-, ^{i}Pr-, and ^{t}Bu-, electron-withdrawing groups such as F-, Cl-, Br-, and CN-, both smoothly afforded the corresponding products **3aj**-**3aq** in good to excellent yields (70-98%). Among them, the structure of alkynylbenzofuran **3ak** was confirmed by X-ray crystallographic analysis. Steric hindrance of the 2-alkynylphenols had no significant effect on reaction. For example, the large sterically hindered 2-((2-isopropylphenyl)ethynyl)phenol **2al**, reacted very well, forming the corresponding product (**3al**) in 95% yield. Excitingly, 2-alkynylphenol **1** bearing heteroaromatics, such as thiophene, was tolerated as well, to give 3-(phenylethynyl)-2-(thiophen-3-yl)benzofuran **3ar** in 86% yield. Furthermore, 2-alkyl-3-(phenylethynyl)benzofurans (**3as**-**3aw**) bearing functional groups such as Ph-, Cl-, HO-, CN-, and NPhth- groups, were accessible in moderate to good yields. Next, we varied the R^1 groups at the benzene core of the 2-alkynylphenol partners (**3ax**-**3bb**), introducing both electron-rich (Me-, Ph-) and electron-poor (F-, Cl-) functional groups. Both groups were tolerated, affording the corresponding alkynylbenzofurans in good to excellent yields (76-92%). However, the benzene ring with a stronger electron-deficient group (MeOCO-) of the 2-alkynylphenol partner, showed a low reactivity, even after extending the reaction time to 48 h, a low yield of alkynylbenzofuran **3az** was obtained (11%, and 65% recovered 2-alkynylphenol **1az**). In addition, by using aliphatic alkynes as coupling partners, a range of 2-alkynylphenols with different functional groups (R^1 and R^2) showed a good tolerance as well, furnishing the target alkynylbenzofurans with yields ranging from 31% to 99% (**3bc**-**3bl**). Of particular note is, that no cyclopropane ring-opening product was observed (**3bl**), which implies that a free radical pathway is not involved.[36]

To further emphasize the general applicability of our strategy, other nucleophilic partners were tested as well. As shown in Fig. 2E, 2-alkynyl tosylaniline **4a** as nucleophilic partner, under standard conditions, furnished the corresponding alkynylative cyclization product **5a** in 94% yield. Moreover, *tert*-butyl-dienoate **4b** as a good nucleophilic precursor, reacted smoothly as well, affording the corresponding product **5b** in 23% yield under standard conditions. Hexa-4,5-dien-1-ol **4c** showed a good tolerance as well, giving the corresponding alkynylation product **5c** in poor yield. It is noteworthy that the efficiency of these reactions can also be improved by optimizing some conditions. For example, by increasing the amount of Au catalyst, phen ligand and coupling partner **2a**, the yields of **5b** and **5c** were significantly higher. This further illustrates the generality and feasibility of the gold-catalyzed alkynylative cyclization strategy by using H_2O_2 as an oxidant.

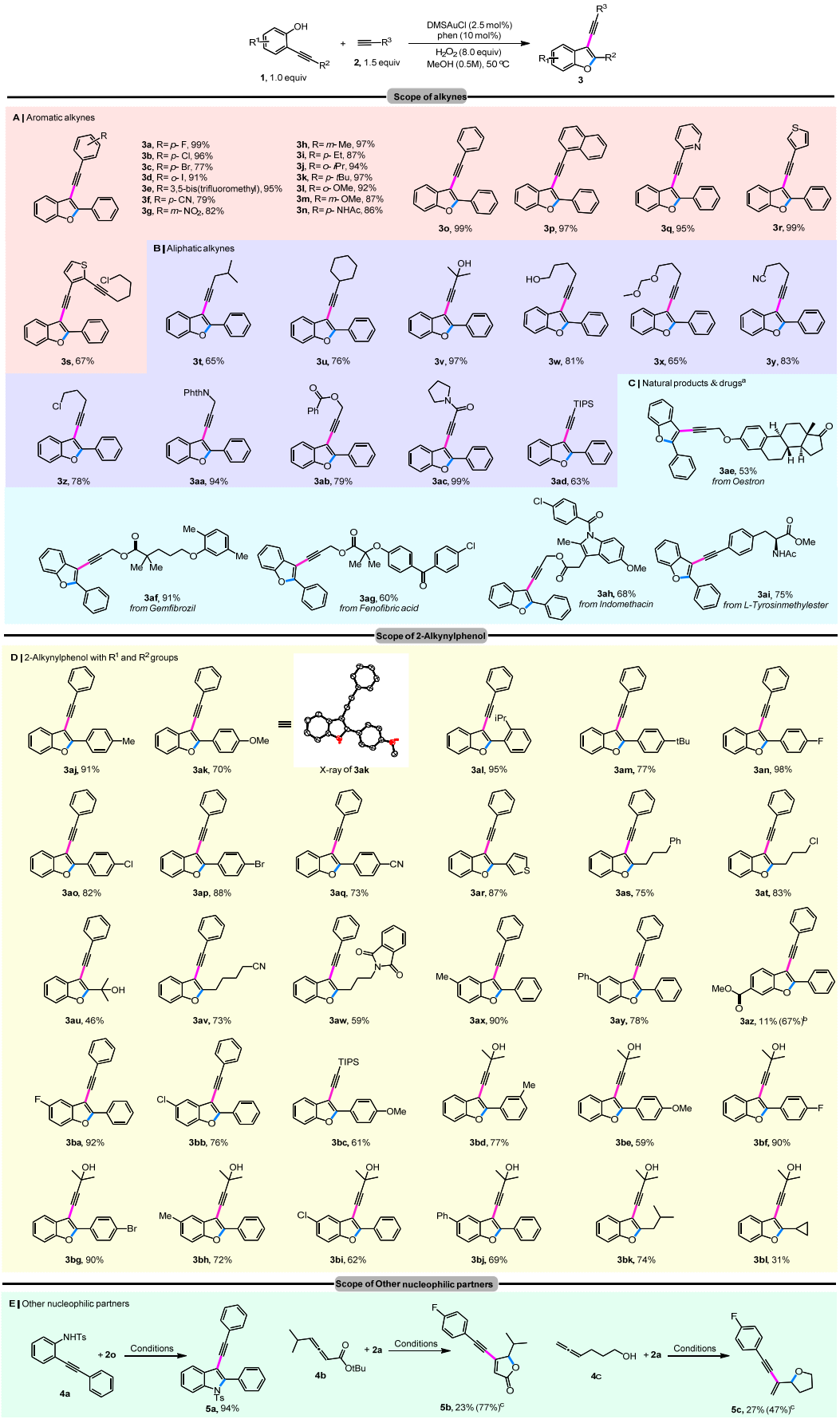


Fig. 2| Scope for the gold-catalyzed alkynylative cyclization. Reaction conditions: 2-alkynylphenol **1**

(0.2 mmol), alkyne **2** (0.3 mmol), DMSAuCl (2.5 mol%), phen (10 mol%), and H_2O_2 (1.6 mmol, 50 wt% in water) in MeOH (0.4 mL), 50 °C. Isolated yields are reported. [a]alkyne **2** (0.21 mmol). [b]Recovered 2-alkynylphenol **1az**. [c]Alkyne **2** (0.4 mmol), DMSAuCl (7.5 mol%), phen (30 mol%).

Synthetic practicality and applications. An upscaling of the reaction to a gram scale was easily possible, which was demonstrated by the synthesis of alkynylbenzofurans **3o** and **3v** that were obtained in yields of 94% and 90% respectively (Fig. 3a). The structural modification of benzofuran as an ubiquitous skeleton of bioactive natural products and pharmaceuticals,[37-39] remains an important field of research. The introduced alkyne moiety in the obtained products of our strategy, offers an attractive synthetic handle for modifications which further multiplies the potential applications. As shown in Fig. 3b, the palladium-catalyzed stereoselective hydrogenation of benzofurans is reported to deliver the corresponding vinylbenzofurans.[12,17] In addition, ethynylbenzofurans as valuable scaffolds, were easily obtained by deprotection of 3-(3-hydroxy-3-methyl)alkynylbenzofurans, such as **3v**. Considering the importance of benzofuran derivatives, we demonstrated a range of post-functional applications to demonstrate the synthetic utility of alkynylbenzofurans (Fig. 3c). The heterotetracene **6b** was efficiently obtained via a $PtCl_2$-catalyzed cyclization.[14] 1,3-Diynylbenzofuran **6c** was successfully obtained by a copper-catalyzed Glaser coupling.[40] In addition, 3-acetylbenzofuran was efficiently synthesized by water addition using $AuCl_3$ as a catalyst. Notably, the unsymmetric dibenzofuranoacetylene **6d** was also efficiently prepared in 79% yield under our standard conditions.

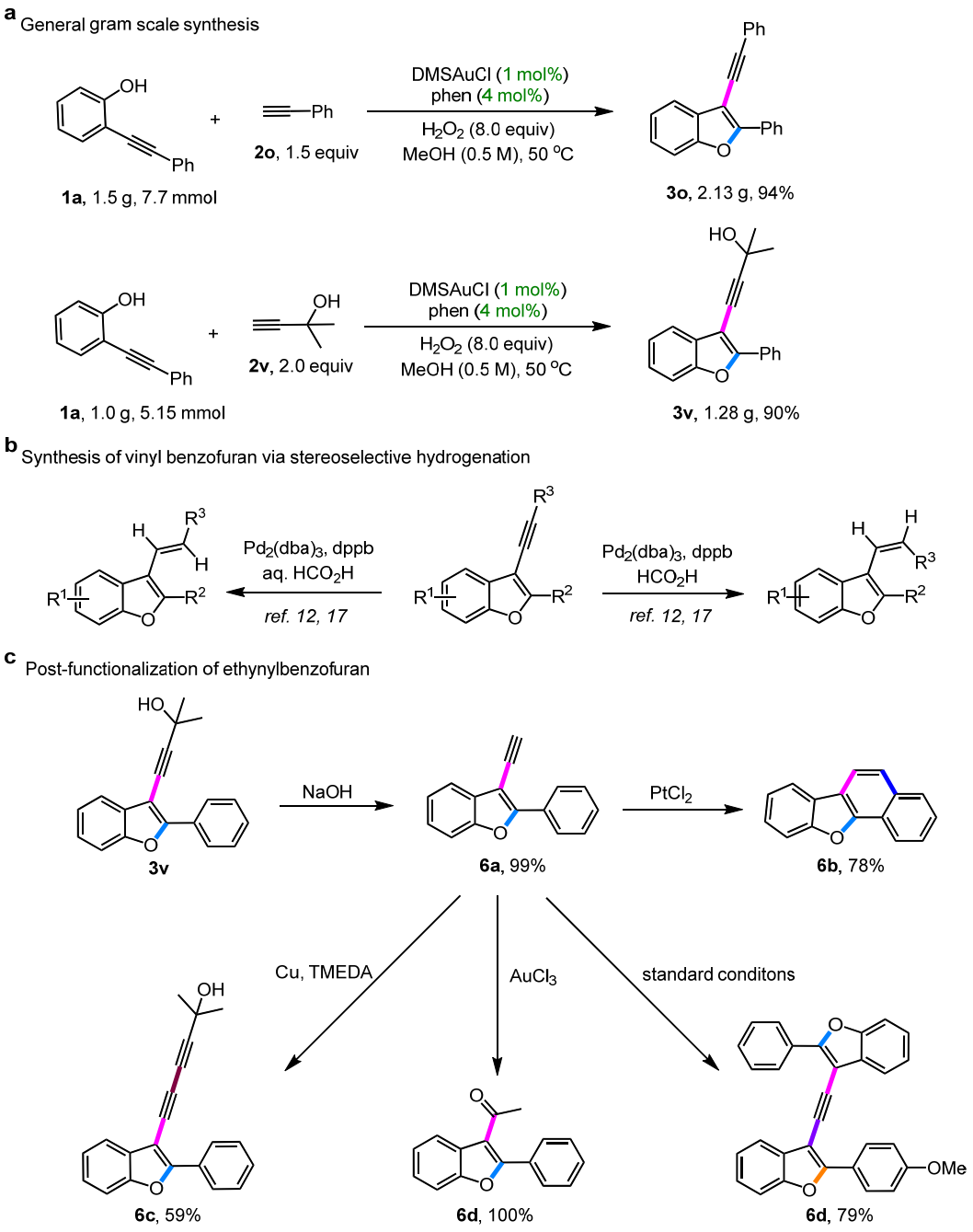


Fig. 3| Comprehensive application. a, General gram scale synthesis. **b**, Synthesis of vinyl benzofuran via stereoselective hydrogenation. **c**, Post-functionalization of ethynylbenzofuran.

Mechanistic studies. To obtain further insight on the operating mechanism, a set of control experiments was conducted (Fig. 4). First, as shown in Fig. 4a, C3-unsubstituted benzofuran **7a** was reacted with 1-ethynyl-4-fluorobenzene **2a** under the normal conditions. This only afforded homocoupling product **7b** after stirring for 72 h, and no alkynylation product **3a** was observed. This finding suggests that an alkynylation of the unfunctionalized benzofuran formed via a prior cyclization- protodemetalation is unlikely in our catalytic system.[14-16]

When stoichiometric amounts of AuCl and phen were reacted with **1a** and **2a** (without any oxidants), neither the alkynylative cyclization product **3a** nor the homocoupling

product **7b** were detected after stirring for 24 h (Fig. 4b, entry 1). By using the same amount of $AuCl_3$ instead of AuCl, a 20% yield of the product **3a** was detected (entry 2). Further addition of excess hydroxide ions via adding KOH, significantly improved the reaction performance, providing **3a** in a 40% yield (entry 3). Interestingly, without phen, no product was detected, and even with the addition of excess KOH formed only trace amounts of product (entries 4 and 5). These results suggest that the gold-catalyzed alkynylative cyclization reaction involves oxidation of Au^{I} to Au^{III} and a reductive elimination in the catalytic cycle. Additionally, the bidentate ligand phen plays a very important role in this reaction, which has significant effect on the reductive eliminations of gold(III) intermediates.[32,41]

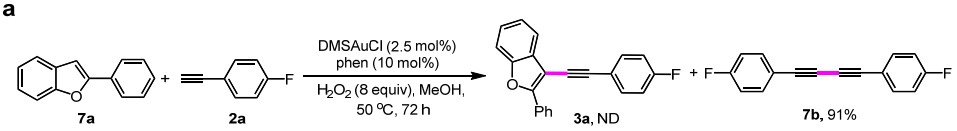
Considering that the catalytic cycle presumably involves vinylgold(I)[10,17-19,42,43] or vinylgold(III)[9,12,44-46] intermediates, we next focused on the formation of the hydrogen-functionalized product **7a**. As shown in Fig. 4c, when DMSAuCl was added (without any ligand and/or additive), only traces of benzofuran **7a** were detected after stirring for 24 h. Interestingly, the addition of phen or H_2O_2, only led to a small amount of product (entries 2 and 3). Under standard conditions (in the absence of a terminal alkyne), the benzofuran **7a** was obtained in a yield of 92% after stirring for 24 h (entry 5). However, after the standard reaction time of 3 h only a small amount of product **7a** was obtained (entry 7). In addition, the replacement of H_2O_2 by H_2O was inefficient (entries 4 and 6). No dimerization product **7c** was detected under these conditions. These results suggest that the catalytic process rather proceeds through a vinylgold(III) intermediate, and the rate of protonation is presumably much slower than the rate of alkynylation.

Several examples of gold-catalyzed oxidative C–C(sp) couplings from terminal alkynes have been reported in the literature.[47-53] There are currently two acceptable mechanisms proposed. One is that the initial *in situ* generation of gold(I)-acetylide **8c** is followed by an oxidation step to form the gold(III)-acetylide intermediate **8d**. As an alternative, Au^{I} is directly oxidized to Au^{III} followed by alkynylation to give the same gold(III)-acetylide **8d**. Considering these two possible pathways, a set of control experiments was carried out (Fig. 4d). Equation 1 shows the experimental results under standard conditions. The stoichiometric reaction of gold(I)-acetylide **8c** (prepared from DMSAuCl and 1-ethynyl-4-fluorobenzene) with 2-(phenylethynyl)phenol **1a**, afforded the product **3a** in 57% yield after stirring for 2 h (equation 2). Even by prolonging the reaction time to 12 h, the yield of **3a** was not significantly improved. Interestingly, when using gold(I)-acetylide **8c** instead of DMSAuCl as the sole gold source, only a low reaction rate was observed after stirring for 2 h, well below the efficiency under standard conditions (equation 3). Furthermore, under standard conditions, the alkynylative cyclization product **3bm** was obtained in a 86% isolated yield, while competition experiment with stochiometric amounts of gold(I)-acetylide **8c**, 2-(phenylethynyl)phenol **1a** and 1-ethynyl-3-fluorobenzene **2bm**, delivered an NMR yield of 78% for the product **3bm** and only 6% for the product **3a** (equations 4 and 5). Based on the above results, and considering that no additional base was added in the catalytic system, the *in situ* generation of gold(I)-acetylide **8c** is unlikely (path A), and Au^{I} is presumably oxidized directly to Au^{III}, which affords vinylgold(III) or gold(III)-acetylide as intermediates.

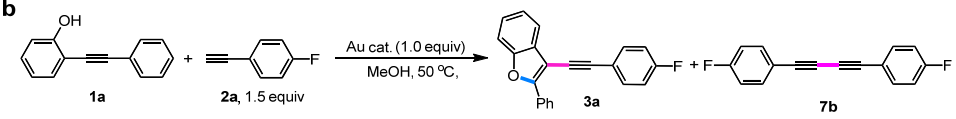
With these preliminary mechanistic investigations in mind, our proposed catalytic

cycle is presented in Fig. 4e. Starting with L_nAu^I salt **A**, oxidation might occur at the stage of the Au^I salt, to afford L_nAu^{III} intermediate **B**. In pathway a, L_nAu^{III} **B** directly activates the alkynes of 2-alkynylphenols **1**, triggering intramolecular cyclization to provide vinylgold(III) intermediate **C**, followed by acetylide formation with alkyne **2** to afford the gold(III)alkynyl complex **D**. Reductive elimination from intermediate **D**, would afford the alkynylation product **3** and regenerate the catalyst. As an alternative, L_nAu^{III} **B** favors to form the gold(III)-acetylide **E** first, followed by activation of the triple bond of 2-alkynylphenols **1** to give the common intermediate **D** (pathway b), which provides product **3** following reductive elimination.

a

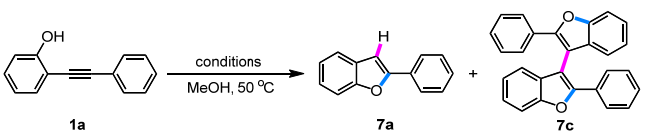


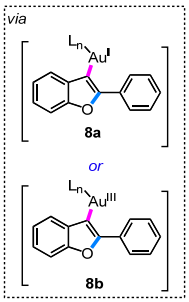
b



Entry	Conditions	3a (%)	7b (%)
1	AuCl, phen (4.0 equiv), 24 h	ND	ND
2	$AuCl_3$, phen (4.0 equiv), 3 h	20%	2%
3	$AuCl_3$, phen (4.0 equiv), KOH (4.0 equiv), 3 h	40%	2%
4	$AuCl_3$, 6 h	ND	ND
5	$AuCl_3$, KOH (4.0 equiv), 6 h	trace	trace

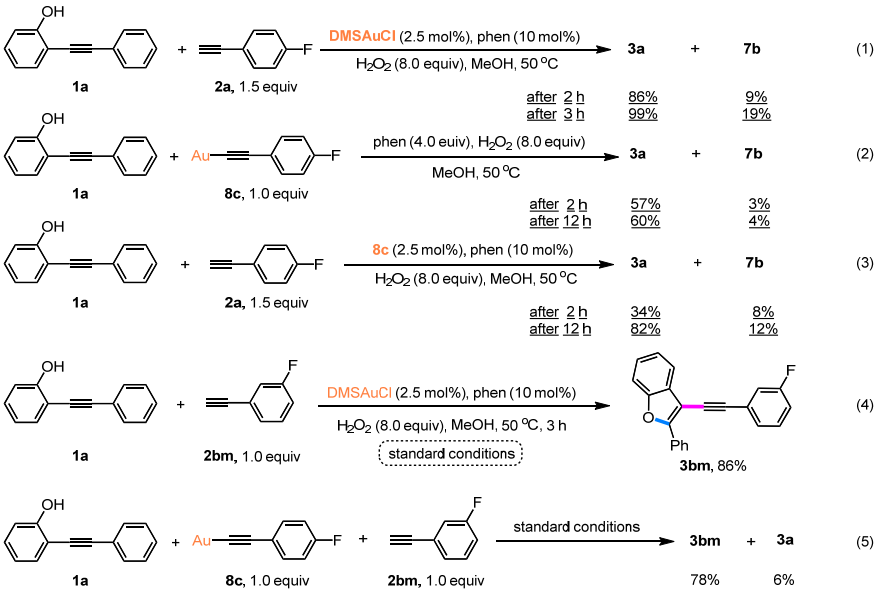
c

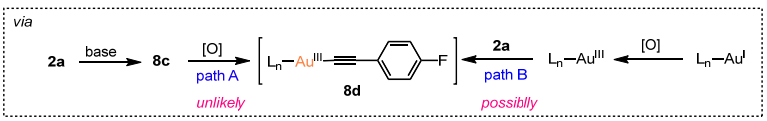




Entry	Conditions	convn (%)	7a (%)	7c (%)
1	DMSAuCl (2.5 mol%), 24 h	< 5	trace	ND
2	DMSAuCl (2.5 mol%), phen (10 mol%), 24 h	11	< 10	ND
3	DMSAuCl (2.5 mol%), H_2O_2 (8.0 equiv), 24 h	13	< 10	ND
4	DMSAuCl (2.5 mol%), water (8.0 equiv), 24 h	< 10	< 5	ND
5	DMSAuCl (2.5 mol%), phen (10 mol%), H_2O_2 (8.0 equiv), 24 h	97	92	ND
6	DMSAuCl (2.5 mol%), phen (10 mol%), water (8.0 equiv), 24 h	12	< 10	ND
7	DMSAuCl (2.5 mol%), phen (10 mol%), H_2O_2 (8.0 equiv), 3 h	15	13	ND

d





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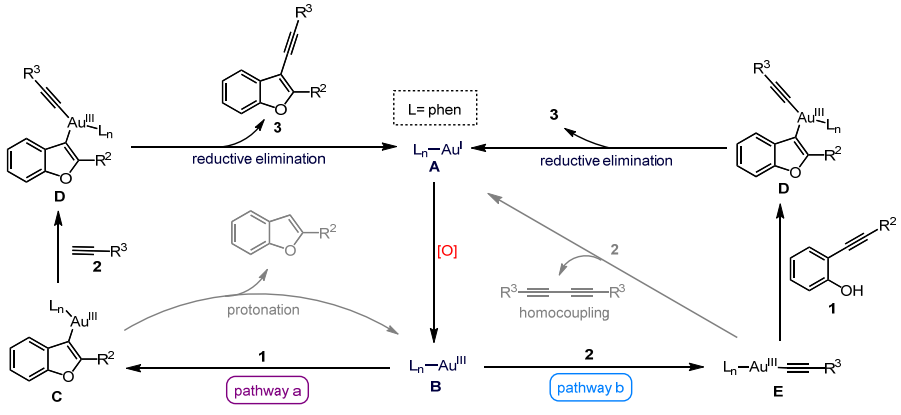

Fig. 4| Mechanistic investigation. a, Exploring the possibility of prior cyclization-protodemetalation. **b,** Exploring possibilities involving the Au^{I}/Au^{III} cycle. **c,** Exploring the possibility of catalytic cycles involving vinylgold(I) or vinylgold(III) intermediates. **d,** Exploring the possibility of catalytic cycles involving gold(I)-acetylide or gold(III)-acetylide intermediates. **e,** Proposed reaction mechanism.

Computational analysis of the proposed mechanism. Based on our findings we propose a possible reaction mechanism in Fig. 4e, which is in line with the thermodynamic data obtained by DFT calculations (Fig. 5). Two potential pathways were considered, both beginning with a ligand replacement of dimethylsulfide by phen in DMSAuCl to form complex **I** in an exergonic reaction step (ΔG = -2.30 kcal/mol). Oxidation with H_2O_2 then yields the *cis*-bishydroxy Au^{III} complex **II** (ΔG = -19.8 kcal/mol), which is thermodynamically more stable than the corresponding *trans*-complex (ΔG = -17.1 kcal/mol). In the pathway a, first the ethynylphenol is deprotonated by one hydroxide ligand of **II**, which dissociates as water. Next, the deprotonated ethynylphenol π-coordinates to the free site *trans* to the phen ligand to furnish **IIIa** in an endergonic reaction step (ΔG = 1.64 kcal/mol). A barrier free cyclization of **IIIa** (ΔG = -41.9 kcal/mol) than delivers the σ-coordinated benzofuran Au^{III} organyl species **IVa**. Next the exergonic formation of Au^{III} acetylide complex **Va (**ΔG = -5.61 kcal/mol) takes place, triggered by the deprotonation of phenylacetylene by the hydroxy ligand, which dissociates as water. At this stage a three membered transition state **TS-a** (ΔG = 15.3 kcal/mol) leads to the formation of a covalent bond between the former acetylide and the benzofuran unit to generate the final product **VI** (ΔG = -52.6 kcal/mol) and regenerate the catalyst **I**. In the pathway b, the *cis*-bishydroxy Au^{III} complex **II** first deprotonates phenylacetylene, which yields a gold(III)-acetylide **IIIb** in an exergonic reaction step (ΔG = -6.01 kcal/mol). In analogy to pathway a, the second hydroxy ligand then triggers the formation of π-complex **IVb** (ΔG = -6.66 kcal/mol) and a barrier free cyclization of the ethynylphenol moiety then furnishes complex **Vb** (ΔG = -33.1 kcal/mol). A related three-membered transition state **TS-b** (ΔG = 17.5 kcal/mol) then delivers the product and regenerates catalyst **I** via reductive elimination (ΔG = -54.9 kcal/mol). As a competing pathway, Au^{III} complex **IIIb** can also form bis-acetylide complex **IVc** (ΔG = -6.50 kcal/mol) in an exergonic reaction, instead of σ,π-complex **IVb**. Transition state **TS-c** (ΔG = 13.7 kcal/mol) then delivers homocoupling product **V** via reductive elimination (ΔG = -56.2 kcal/mol). Indeed, this species was detected as side product under some conditions (such as Fig. 4d).

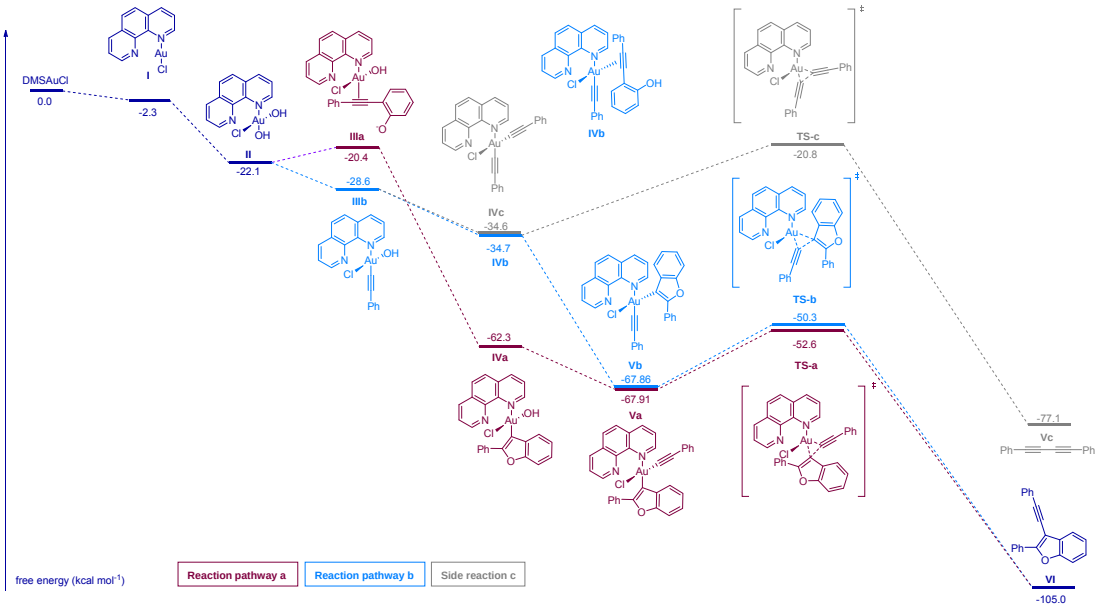

Fig. 5| Calculated reaction pathways and energy landscape for gold-catalyzed alkynylative cyclization. The geometries of all possible intermediates were first optimized, followed by frequency analyses on a B3LYP[54-57]/def2-SVP[58] level of theory. For gold, additionally the basis set def2-TZVP[58] was applied.

Conclusion

In conclusion, we report the first example of using H_2O_2 as an oxidant to achieve a gold-catalyzed alkynylative cyclization with terminal alkynes. Through this method, an efficient synthesis of 3-alkynylbenzofurans from terminal alkynes was achieved. The reaction system exhibits the advantages of high atom economy, low synthetic costs, mild reaction conditions, remarkable selectivity, wide substrate scope and good functional group tolerance. Control experiments with other commonly used oxidants were not effective with revealed that this process is not only a more attractive substitute of common methodologies, but instead offers a unique tool for gold catalysis. In addition, this method was not only limited to the synthesis of 3-alkynylbenzofurans and it could also be applied to other forms of alkynylative cyclization reactions. We propose two possible reaction mechanisms based on mechanistic experiments, which are consistent with the results of DFT calculations. This reaction involves the Au^{I}/Au^{III} catalytic cycle, and 1,10-phenanthroline (phen) as a bidentate ligand is crucial for the catalytic cycle, since it shows a significant influence on the oxidation process of Au^{I} to Au^{III} and reductive eliminations of Au^{III} intermediates. As a cheap and green oxidant, H_2O_2 has great potential for Au^{I}/Au^{III} redox catalysis and opens up a new dimension of gold catalysis. We also expect that this method will provide valuable inspiration for the design of other homogeneously gold-catalyzed oxidative coupling reactions with H_2O_2 as an oxidant.

Methods

General procedure for the gold-catalyzed alkynylative cyclization with terminal alkynes using H_2O_2 as oxidant. A 4-mL vial equipped with a magnetic stir bar was charged with DMSAuCl (1.5 mg, 2.5 mol%), 1,10-phenanthroline (3.6 mg, 10 mol%), 2-(alkynyl)phenol **1** (0.2 mmol, if as solid), terminal alkyne **2** (0.3 mmol, 1.5 equiv, if as solid) in MeOH (0.4 mL), then 2-(alkynyl)phenol **1** (0.2 mmol, if as oil), terminal alkyne **2** (0.3 mmol, 1.5 equiv, if as oil) and H_2O_2 (89.6 μL, 1.6 mmol, 50 wt% in water) were added.

The mixture was stirred at 50 °C. After completion of the reaction (monitored by TLC), the resulting solution was cooled to room temperature. 2.0 mL DCM was added, the solution was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual mixture was purified by column chromatography on silica gel, to afford the crude products.

Data availability

The findings of this study are available within the paper and its Supplementary Information. Crystallographic parameters for compound **3ak** is available free of charge from the Cambridge Crystallographic Data Centre under CCDC 2180908 (**3ak**), respectively. All data are available from the authors upon reasonable request.

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Author contributions

H. Shi designed, carried out the main part of the experiments, and analyzed data; M. C. Dietl conducted the computational calculations; P. M. Stein, T. Wang and J. Li contributed several experiments; P. Krämer analyzed IR data; F. Rominger conducted X-ray crystal structure analysis; All authors participated in discussion; H. Shi, M. C. Dietl, M. Rudolph, and A. S. K. Hashmi co-wrote the paper; A. S. K. Hashmi initiated the project.

Conflicts of interest

The authors declare no conflict of interest.