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Gold(I)-catalyzed and Nucleophile-guided Ligand-directed Divergent Synthesis

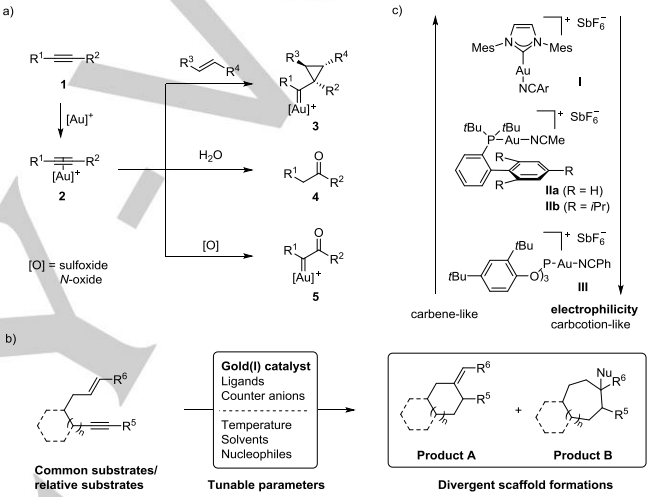
Yen-Chun Lee[a,b], Lena Knauer[b], Kathrin Louven[b], Christopher Golz[b], Carsten Strohmann[b], Herbert Waldmann*[a,b] and Kamal Kumar*[a]

Dedicated to Prof. Manfred T. Reetz on the occasion of his 75th birthday

Abstract: Transition metal catalysts can mediate a plethora of skeleton rearrangements of a range of substrates to construct complex small molecules. Yet, their potential to transform common substrates into distinct molecular scaffolds has not been fully explored to deliver biologically relevant small molecules. Gold(I)-catalyzed transformations of enynes are amongst the most intriguing rearrangements and provide opportunities to access a range of diverse scaffolds efficiently. In ligand-directed divergent synthesis (LDS), variation of ligands in metal complexes determines the fate of substrates during their transformation into distinct scaffolds. For instance, variation of ligands in gold(I) catalysts helps oxindole derived 1,6-enynes transform into a number of distinct molecular frameworks. In this report, we present how variation in ligands in gold(I) catalysts, nucleophile-additives and alkyl and alkynyl substitutions on the 1,6-enynes as well as replacement of the oxindole ring with a different privileged ring-system (PRS) influence the LDS approach to access wider chemical space. Based on the results, we propose several mechanistic pathways in gold(I)-catalyzed cycloisomerizations and cascade reactions of 1,6-enyne substrates leading to structurally distinct chemotypes.

Introduction

The unique alkynophilicity of cationic gold(I) catalysts has been exploited as a powerful tool to construct structurally complex molecular frameworks, which otherwise represent difficult synthetic challenges.[1] In many cases, gold(I) catalysis has successfully offered synthetic access to natural product-based[2] or -inspired small molecules[3]. Mechanistically, the electrophilic character of alkyne substrates (**1**) is enhanced when the cationic gold(I) catalyst first coordinates the acetylene moiety (**2**) followed by nucleophilic addition to the ensuing gold(I)-acetylene complexes (**2**). Often, this addition further triggers a range of different transformations *via* cascade type reactions.[4] For example, interaction of gold(I) activated acetylenes (**2**) with olefins may lead to cyclopropyl gold carbene intermediates (**3**).[5] In the presence of H_2O, the gold(I) activated acetylenes (**2**) may simply produce alkyne hydration products (**4**).[6] In case, sulfoxides[7] or *N*-oxides[8] are used, the reaction may lead to reactive α-oxo gold carbene intermediates (**5**, Scheme 1a) which offer new opportunities for developing new synthetic methods.[9]



Scheme 1. a) Nucleophilic addition to gold(I) activated acetylene leading to different transformations. b) Gold(I)-catalyzed divergent scaffold synthesis. c) Relative electrophilicity of gold(I) catalysts. Mes = 2.4.6-trimethylphenyl, *t*Bu = *tert*-butyl, *i*Pr = *iso*-propyl.

One of the most attractive features of cationic gold(I) catalysis is that introducing subtle changes to the reaction conditions, for instance, varying solvents,[10] ligands,[11] counter ions[12] or additives,[13] can lead to structurally distinct products (Scheme 1b).[14] Recently, we reported a ligand-directed divergent synthesis (LDS) approach wherein varying ligands around a metal center guides the catalytic reactions into different pathways to form distinct chemotypes.[15] Both the electronic and the steric features of ligands in gold(I) complexes can influence the reaction pathways of enyne substrates (Scheme 1c).[16] For instance, catalyst (**I**) with electron-rich ligands, like *N*-heterocyclic carbenes (NHC),[17] may prefer to form carbene type intermediates in the transformation of enynes while a gold complex (**III**) with electron-deficient ligands, like phosphites may favor formation of carbocation type intermediates.[18] Similarly, the steric bulk of the ligand in gold complexes may guide a reaction intermediate to either follow or avoid a certain reaction pathway and thereby leading to selective formation of a particular molecular scaffold.[19] By fine tuning the parameters in ligands, oxindole based crotylated 1,6-enyne (**6a**) was transformed into

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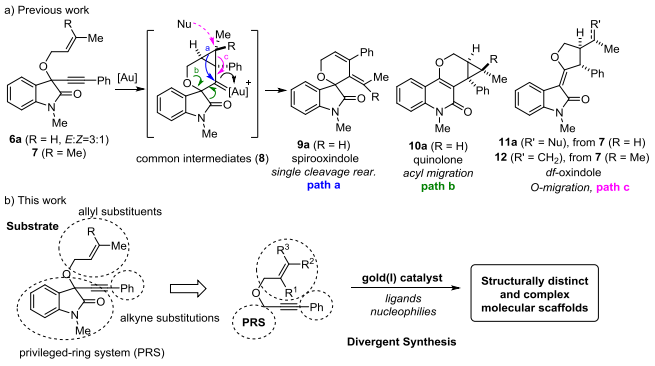


Scheme 2. a) Gold(I)-based ligand-directed divergent synthesis on oxindole derived 1,6-enyne system. b) Variation of allyl substitutions and privileged-ring system in gold(I)-catalyzed divergent scaffold synthesis. Me = methyl, Ph = phenyl, Nu = nucleophile.

three structurally distinct scaffolds, spiro-oxindole (**9a**), quinolone (**10a**), and dihydrofuranyl oxindole (*df*-oxindoles, **11a**). The key transformations of the common intermediates (**8**) *i.e.* single cleavage rearrangement (cyclopropane migration),[20] pinacol type rearrangement (acyl group migration),[21] and *O*-migration (cyclopropane opening),[22] respectively led to the selective formation of distinct scaffolds of **9**, **10** and **11** (Scheme 2a).[15] In this gold(I)-catalyzed enyne cycloisomerizations, allyl substitutions also play an important role in guiding the gold-carbene intermediates (**8**) to from diverse products. For instance, by changing the crotyl- to a prenyl group in the oxindole based 1,6-enyne (**7**), the gold(I)-catalyzed reaction became selective towards *df*-oxindoles (**12**) supporting an *iso*-propenyl group. We now report the further investigation of the potential diversifications of 1,6-enynes into interesting new scaffolds by inducing variations in enyne substitutions, addition of external nucleophiles, and by replacing oxindole with another privileged ring-systems (PRS)[23] to gain access to a wider chemical space (Scheme 2b).[24]

Results and Discussion

Oxindole derived 1,6-enynes with various allyl substitutions

We had observed that treating crotyl ether enyne substrate **6a** (*E*:*Z* = 3:1) with 5 mol% of a cationic gold(I) catalyst with different ligands could selectively provide spirooxindole **9a** and quinolone **10a** in good yields (Table1, entries 1-3).[15] The cycloisomerization cascade catalysed by NHC-gold(I) catalyst (**I**) delivered a spirooxindole **9a** as the major product in 43% yield along with quinolone **10a** in 7% yield. (*Z*)-**6a** was recovered as well in 27% (entry 1). The selectivity of the reaction could be tuned toward quinolone **10a** formation by using bulky phosphine gold(I) catalyst (**IIb**). In this case, quinolone **10a** was formed in 67% yield and a minor epimeric product (*epi*-**10a**, R^2 = H, R^3 = Me) was obtained in 20% yield (entry 2). The gold(I) catalyst with electron-deficient phosphite ligand (**III**) also provided spirooxindole **9a** as the major product in 60% yield. The recovery of 10% recovery of (*Z*)-**6a** (entry 3) suggests that the reactivity of (*Z*)-**6a** might differ from (*E*)-**6a** under these reaction conditions.

The scope of the ligand directed enyne cycloisomerization was further investigated by employing (*E*)-enyne (**6b**) and (*Z*)-enyne (**6c**) with ethyl substituent (entry 4-9). All reactions were carried out at 0.1 molar concentration of enyne substrate in dichloromethane (DCM) and using 5 mol% of gold (I) catalyst (Table 1). When treated with catalyst **I**, the (*E*)-isomer of **6b** provided spirooxindole (**9b**) in 79% yield that further improved to 88% with a phosphite gold(I) catalyst (**III**) (entries 4-5). The bulky phosphine gold(I) catalyst (**IIb**) altered the reaction pathway and afforded the quinolone (**10b**) as the major product in 40% yield (entry 6). However, in contrast to divergent transformations of (*E*)-enyne **6b** into spirooxindole (**9b**) and quinolone (**10b**), the (*Z*)-enyne **6c** afforded only quinolone **10c** as the major product with all three catalytic gold(I) complexes (entries 7-9). These results clearly suggest the key role of the (*E*)- and (*Z*)-stereochemistry of the olefinic part of enynes in directing the reaction intermediates into distinct chemotypes (**9** and **10,** *vide infra*).

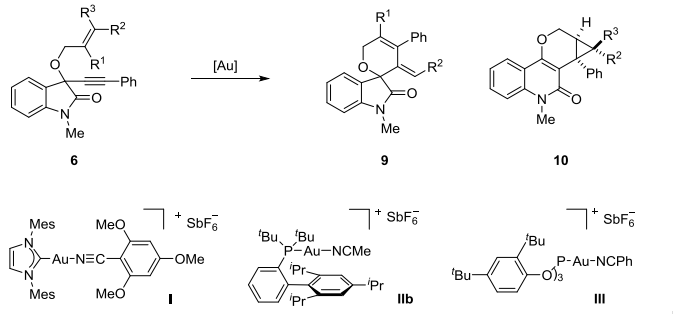
Furthermore, oxindole based 1,6-enynes with variations on the alkene part (**6d-f**) were subjected to cycloisomerizations catalysed by gold complexes **I**, **IIb** and **III**. Replacing the ethyl group by a bulkier phenyl as R^2, 1,6-enyne **6d** favoured quinolone formation under NHC-gold(I) complex (**I**)-catalysed reaction condition, and **10d** was formed in 40% yield (entry 10). However, treating **6d** with gold(I) catalyst **IIb** and **III** led to the formation of a complex mixture (entry 11-12). Interestingly, allylic 1,6-enyne (**6e**) appeared to be inert to the gold(I) catalyst **I** and, with catalyst **III** delivered a complex-product mixture. The phosphine-gold(I) catalyst (**IIb**) induced enyne cycloisomerization of **6e** to give quinolone **10e** in 56% yield (entry 13-15).

Substitution at the R^1 position of the olefin in enynes **6** is very critical and can introduce steric problems for some intermediates. This was evident from the gold(I)-catalyzed cycloisomerization reactions of enyne **6f** (R^1 = Me). While the NHC-gold(I) catalyst (**I**) did not give any product in the reaction with **6f** and led to recovery of the starting material, gold(I) complexes with a phosphine or phosphite (**II** and **III** respectively) afforded only the spirooxindole (**9f**) *albeit* in low yields (entry 17-18). The yield of the spirooxindole **9f** was slightly improved to 46% by using phosphine-gold(I) catalyst (**IIb**) and diethyl ether as solvent (entry 19). The relative stereochemistry in **9f** was corroborated by single crystal X-ray structure analysis (Supporting information).

Analyzing the ligand-directed gold-catalyzed cycloisomerization reaction of 1,6-enynes bearing different allyl substitutions, we observed that formation of spirooxindole and quinolone was affected both by olefin substitutions as well as the ligands in catalytic complexes (Scheme 3). Transformations leading to spirooxindoles (**9**) and quinolones (**10**) share common intermediates (**8**) formed after the gold(I)-catalyzed 6-*endo*-dig cyclization of 1,6-enynes (**6**). In spirooxindole formation, intermediates (**8**) undergo cyclopropane migration to give cationic intermediates (**13**), a process that is favored by NHC-

and phosphite gold complexes to transform (*E*)-**6** enyne into spirooxindoles (entries 1 and 3, Table 1).[20]

Table 1. Ligand variations in gold(I)-catalyzed divergent scaffold synthesis with different allyl substitutions.



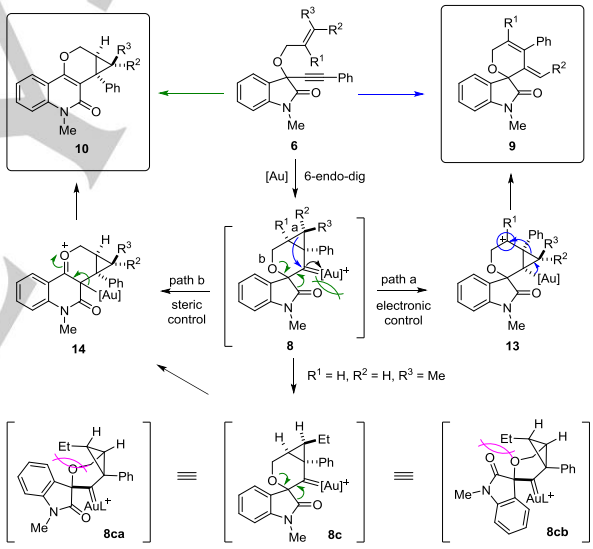
Entry[a]	6	R^1	R^2	R^3	[Au]	product	Yield (%)
1[b]	**6a**	H	Me	H	**I**	**9a**[c]	43
2[b]	**6a**	H	Me	H	**IIb**	**10a**[d]	67
3[b]	**6a**	H	Me	H	**III**	**9a**[e]	60
4	**6b**	H	Et	H	**I**	**9b**	79
5	**6b**	H	Et	H	**III**	**9b**	88
6	**6b**	H	Et	H	**IIb**	**10b**	40
7	**6c**	H	H	Et	**I**	**10c**	58
8	**6c**	H	H	Et	**IIb**	**10c**	37
9	**6c**	H	H	Et	**III**	**10c**	63
10	**6d**	H	Ph	H	**I**	**10d**	40
11	**6d**	H	Ph	H	**IIb**	-[f]	-
12	**6d**	H	Ph	H	**III**	-[f]	-
13	**6e**	H	H	H	**I**	-[g]	-
14	**6e**	H	H	H	**IIb**	**10e**	56
15	**6e**	H	H	H	**III**	-[f]	-
16	**6f**	Me	H	H	**I**	-[g]	-
17	**6f**	Me	H	H	**IIb**	**9f**	37
18	**6f**	Me	H	H	**III**	**9f**	17
19[h]	**6f**	Me	H	H	**IIb**	**9f**	46

[a] Reaction condition: [Au] 5 mol%, DCM (0.1 M), rt, overnight; [b] *E*:*Z* = 3:1. [c] **10a** was obtained in 7% yield and (*Z*)-**6a** was in 27% recovery; [d] *epi*-**10a** (R^2 = H, R^3 = Me) was obtained in 20% yield; [e] (*Z*)-**6a** was in 10% recovery; [f] Complex mixture formation; [g] Starting material recovery; [h] Solvent is diethyl ether.

Plausibly, the cationic intermediates subsequently eliminate the gold(I) catalyst to open up the cyclopropane ring, giving spirooxindoles **9a**/**9b** as products (Scheme 3, blue arrow). With methallyl substrate (**6f**, R^1 = Me), the cationic intermediate is stabilized as 3° carbocation (**13f**), and therefore gold(I)-catalyzed cycloisomerization selectively give spirooxindole (**9f**) as product (Table 1, entry 17-19).

In order to steer the intermediate into a ring-expanded quinolone, steric hindrance between substrate and catalyst plays a decisive role. Therefore, gold(I)-complex (**IIb**) supporting bulky ligand drives the pinacol type ring expansion of the **8** leading to oxocarbenium intermediates (**14**). The deauration of the latter provides the quinolones (**10**, Scheme 3, green arrow, and Table 1, entry 2, 6 and 14).[25]

Notably, for (*Z*)-1,6-enynes, for instance **6c,** the steric repulsion of alkyl substitution (Et) at the R^3 position and spiro-ring system may generate a disfavorable strain in the intermediate (**8ca** and **8cb**, Scheme 3), and thus inducing the ring-expansion of the oxindole (**8c**) leading to the selective formation of quinolones as observed for all three gold catalysts (**I**-**III**, entries 7-9, Table 1 and Scheme 3). Substrates with phenyl at R^2 could undergo this ring expansion reaction as well, though only NHC-gold catalyst **I** provided the desired product (**I**, Table 1, entry 10).

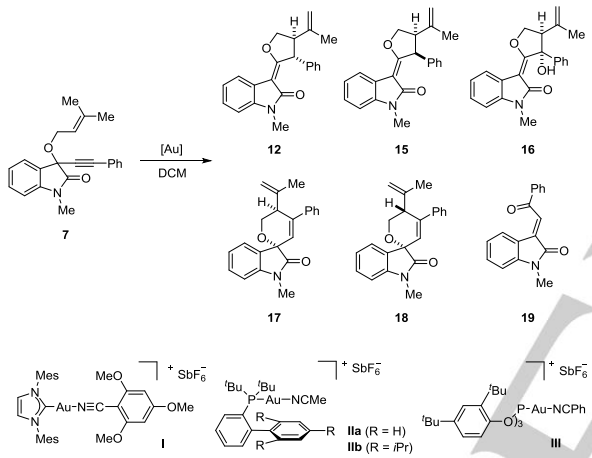


Scheme 3. Proposed reaction mechanisms of spirooxindole **9** and quinolone **10** formation.

As compared to enynes **6a**-**f**, prenylated substrates **7** exhibited a different pattern of transformations under the influence of gold catalysts (Table 2). Surprisingly, when *in situ* generated $Ph_3PAuOTf$ was used as catalyst (10 mol%), substrate **7** provided six different products, *i.e*. *df*-oxindoles (**12** in 8% yield, **15** in 26% yield, and **16** in 5% yield), spirooxindoles (**17** in 16% yield and **18** in 12% yield), and Meyer-Schuster rearrangement (MS) product (**19** in 7% yield, entry 1)[6a]. Except for the MS product, the relative configuration of the other products, **12**, **15**, **16**, **17**, and **18** were determined by single crystal X-ray structure analysis (Supporting information). Moreover, under standard reaction conditions, no reaction was

recorded with NHC-gold(I) catalyst (**I**, entry 2). However, at higher concentration (0.2 M), a complex mixture was observed (entry 3). Fortunately, treating **7** with a gold(I) catalyst with bulky phosphine ligand (**IIa**) led to a full conversion of starting material and *trans-df*-oxindole (**12**) was formed in 50% yield (entry 4). Changing the solvent from DCM to THF further improved the yield of *trans-df*-oxindole (**12**) to 91% (entry 5). When gold(I) complex with sterically bulky phosphine ligand (**IIb**) was used, a slightly lower yield of *df*-oxindole was obtained (entry 6). In the presence of phosphite-gold(I) catalyst (**III**), 40% of the substrate enyne was recovered, along with formation of *trans-df*-oxindole (**12**) and spirooxindoles (**17**, **18**) in 17%, 30% and 13% yield, respectively (entry 7). Thus, treating **7** with catalyst **IIa** in THF provided an ideal condition to selectively transform enyne **7** into *df*-oxindole **12**.

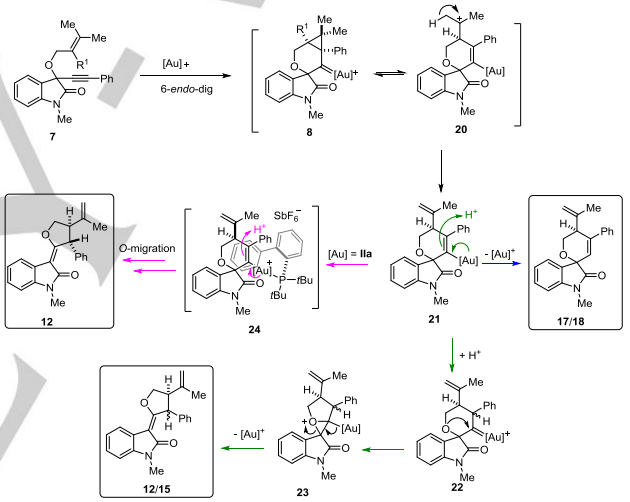
Table 2. Ligand variations in gold(I)-catalyzed divergent scaffold synthesis with oxindole-based prenylated 1,6-enyne.



Entry[a]	[Au] (mol%)	Yield (%)					
		12	**15**	**16**	**17**	**18**	**19**
1	$Ph_3PAuOTf$ (10)	8	26	5	16	12	7
2	**I** (5)	-[b]	-	-	-	-	-
3[c]	**I** (5)	-[d]	-	-	-	-	-
4	**IIa** (5)	50	-	-	-	-	-
5[e]	**IIa** (5)	**91**	-	-	-	-	-
6	**IIb** (5)	49	-	-	-	-	-
7[f]	**III** (5)	17	-	-	30	13	-

[a] Reaction condition: [Au] 5 mol%, DCM (0.1 M), r t, overnight; [b] starting material recovery; [c] DCM (0.2 M); [d] Complex mixture formation; [e] THF was used as solvent; [f] enyne **7** recovered (40%).

Mechanistically, gem-dimethyl groups in prenylated enyne substrate **7** may help generate a stabilized 3°-carbocation intermediate (**20**) after gold(I)-catalyzed 6-*endo*-dig cyclization (Scheme 4). This relatively stable carbocation (**20**) undergoes a proton elimination to provide a common intermediate (**21**) for the formation of diverse products. Direct protodeauration of the vinyl gold intermediate (**21**) gives diastereomeric spirooxindoles (**17** and **18**, blue arrow). In an alternative reaction pathway, non-stereoselective protonation generates gold carbene intermediates (**22**). Subsequently, insertion of an ether oxygen to the gold carbene leads to highly strained oxonium intermediates (**23**) that concomitantly rearrange to diastereomeric *df*-oxindoles (**12** and **15**) as products (green arrow).[22] The selectivity of product formation can be significantly improved by employing a bulky phosphine ligand in gold complex (**IIb**). With the catalyst **IIb**, the direct protodeauration of the vinyl gold intermediate was completely prohibited as the biphenyl group in phosphine ligand blocks the sterically less hindered face and directs a stereoselective protonation (**24**). In this scenario, the *trans-df*-oxindole (**12**) was obtained exclusively in good yield (magenta arrow).



Scheme 4. Proposed reaction mechanisms of gold(I) catalysed cycloisomerization of oxindole derived prenylated 1,6-enyne (**7**).

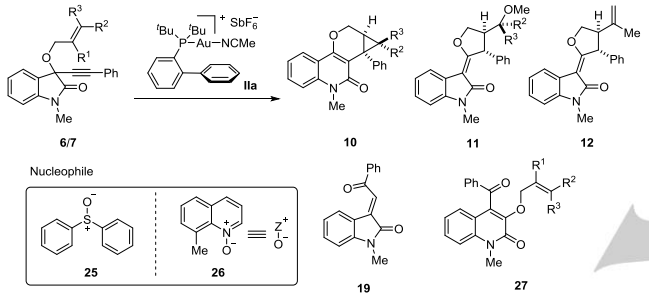
Enyne-cycloisomerizations in the presence of external nucleophiles

The alkynophilic gold(I) catalyst enhances the electrophilic nature of acetylene moiety in enyne substrates and thus may invite an intramolecular nucleophilic attack by a proximal electron-rich olefin, and subsequently follows various skeleton rearrangements.[22] Moreover, if external nucleophiles are present, they can also add to the gold-activated intermediates and deliver structurally distinct products. With a series of 1,6-enynes (**6a-f**, and **7**) in hand, we utilized alcohol (MeOH), sulfoxide (**25**), and *N*-oxide (**26**) as representative external nucleophiles and phosphine-gold(I) complex (**IIa**) as the catalyst to achieve a nucleophile-guided divergent scaffold synthesis (Table 3).

In the presence of methanol as nucleophile, the crotylated 1,6-enynes **6a-b** (*E*:*Z* = 3:1) afforded the *df*-oxindoles (**11a-b**) in

73 and 67% yields respectively along with minor MS product (**19**, entries 1-2, Table 3). When (*Z*)-**6c** was employed in the same reaction, the MS product (**17**) was formed as the major product (67%) and the *df*-oxindole **11c** was obtained in only 20% yield (entry 3). Thus, enyne substrates with (*E*)-olefin favored the formation of *df*-oxindoles. Even when steric bulk was enhanced by introducing phenyl group as R^2 (**6d**), the reaction smoothly delivered the *df*-oxindole **11d** in 56% yield (entry 4). However, allyl substituted enyne **6e** did not follow the desired cycloisomerization and the MS product (**17**) was the only product formed in this reaction (entry 5). β-Methallyl 1,6- enyne substrate (**6f**) yielded an inseparable complex mixture of products (entry 6). Prenylated substrate (**7**) nicely and expectedly provided the corresponding *df*-oxindole (**11g**) in 66% yield, though isopropenyl-*df*-oxindole (**12**) was also isolated in 23% yield (entry 7).

Table 3. Variations of allyl substitutions and nucleophiles in gold(I)-catalyzed divergent scaffold synthesis.



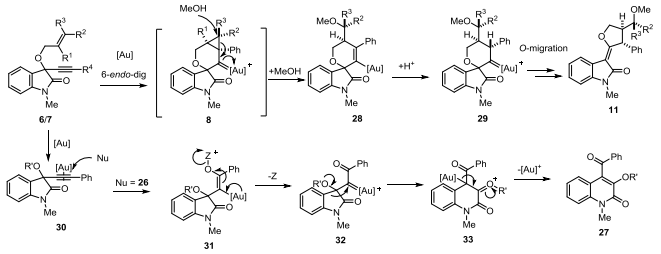
Entry[a]	6/7	R^1	R^2	R^3	Nu.[b]	Yield (%)				
						10	**11**	**12**	**19**	**27**
1[c]	**6a**	H	Me	H	MeOH		73		18	
2	**6b**	H	Et	H	MeOH		67		15	
3	**6c**	H	H	Et	MeOH		20		67	
4	**6d**	H	Ph	H	MeOH		56		8	
5	**6e**	H	H	H	MeOH				86	
6	**6f**	Me	H	H	MeOH	-[d]				
7	**7**	H	Me	Me	MeOH		66[e]	23		
8	**6b**	H	Et	H	**25**	60				
9	**6b**	H	Et	H	**26**					83
10	**6b**	H	Et	H	MeOH + **26**					70

[a] Reaction condition: catalyst **IIa** 5 mol%, DCE (0.1 M), 60 °C, overnight; [b] Amount of nucleophile: MeOH (10 eq), **25** (2 eq), **26** (1.1 eq); [c] *E*:*Z* = 3:1; [d] complex mixture was formed; [e] **11g**

In order to further unravel distinctive transformations guided by nucleophiles, sulfoxide (**25**) and quinoline-*N*-oxide (**26**) endowed with nucleophilic and oxidant nature were employed in the gold(I)-catalyzed transformations (entry 8-10). Notably, these reagents are frequently utilized for oxidizing the gold carbene intermediate to form a carbonyl functionality or react with gold(I) activated acetylene to give α-oxo gold carbene, a reactive intermediate, which may undergo oxidative cyclization or skeleton rearrangements (Scheme 1a).[26] In our screening, the oxygen addition product was not formed when (*E*)-enyne **6b** was treated with 2 equivalents of diphenyl sulfoxide **25**, *albeit* quinolone **10b** was isolated in 60% yield (entry 8). Resorting to *N*-oxide **26** as oxidative nucleophile, **6b** successfully gave an oxygen addition product **27** in 83% yield (entry 9). In a competition experiment the 1,6-enyne **6b** was exposed to methanol, and *N*-oxide **26**, under gold(I) catalysis. The reaction afforded **10b** as single product in 70% yield (entry 10) demonstrating that *N*-oxide **26** is the most favorable nucleophile to react with the activated acetylene under the presented gold(I)-catalyzed reaction condition.

Mechanistically, in gold(I)-catalyzed reactions of enynes, external nucleophiles can either add to one of the enyne-cycloisomerization gold carbene intermediates or simply to the gold(I) activated acetylene moiety. In the former case, 1,4-addition of methanol to the cyclopropane gold carbene intermediate (**8**) forms the *df*-oxindole vinyl gold species **28** (Scheme 5). After stereoselective protonation of **28**, the resulting gold carbene intermediate (**29**) follows the *O*-migration cascade to give methoxy adduct of *df*-oxindole (**11**, Scheme 5). In the second case, methanol may add to the gold(I) activated acetylene and follows a MS rearrangement to give an oxindole (**19**, Scheme 5).[6a] These two reactions compete with each other and in particular are influenced by the nucleophilicity or electron-rich nature of the olefin moiety in enyne substrates. Therefore, enyne (**7**) with nucleophilic trisubstituted olefin quickly followed the cycloisomerization before methanol could trap the gold(I) activated acetylene to give the MS product (**19**), and led to form methoxyl-*df*-oxindole (**11g**, Table 3, entry 7) via intermediate (**8**). Most of the disubstituted olefin substrates afforded a mixture of methoxy-*df*-oxindoles (**11**) and the MS product (**19**, entry 1-4), except for substrate **6f** (entry 6). Likewise, the mono-substituted, as relatively electron-poor olefin substrate (**6e**), exclusively provided the MS product **19** (entry 5).

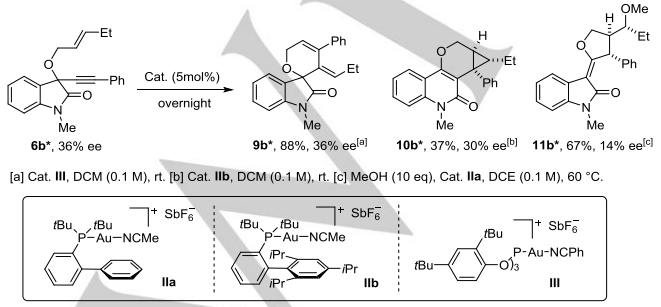
The oxidative nucleophile *N*-oxide **26** also reacted with the gold(I) activated acetylene and triggered a rearrangement cascade leading to quinolone **27** (Scheme 5). Mechanistically, we assume that after the nucleophilic addition of *N*-oxide **26**, the quinoline segment of *N*-oxide (**Z**) is eliminated from the vinyl gold intermediate (**31**) and α-oxo gold carbene (**32**) is generated. Subsequently, pinacol type rearrangement leads to ring expansion and deauration closes the catalytic cycle to yield quinolone (**27**, Scheme 5).[27]



Scheme 5. Proposed reaction mechanisms of nucleophiles-guided gold(I) catalysed cycloisomerizations of oxindole derived 1,6-enynes.

Chirality transfer

The proposed reaction mechanisms of ligand-directed gold(I)-catalyzed cycloisomerization of oxindole based 1,6-enynes depicts **8** as the initial intermediate leading to the formation of spirooxindole, quinolone as well as *df*-oxindole scaffolds (Scheme 3 - 5) and understandably plays a crucial role in establishing all the stereogenic centers in the final products. Therefore, we were curious to determine the influence of the spirocenter in enantiomerically enriched substrates on the newly generated stereogenic centers in the gold(I)-catalyzed cycloisomerizations. To this end, experiments were initiated by preparation of optically enriched (*E*)-enyne **6b*** (36% enantiomeric excess, ee), employing a $Zn(OTf)_2$-catalyzed enantioselective alkylation (see Supporting information).[28] In the gold(I)-mediated reaction leading to spirooxindole (**9b***), the chirality was maintained as 36% ee. Thus, in this particular reaction, no epimerization at the spirocarbon occurs during the cycloisomerization cascade. The enantiomeric excess, however, slightly decreased from 36% to 30% when 1,6-enyne **6b** followed the quinolone formation (**10b***) and further drastically decreased to 14% during its transformation into the *df*-oxindole formation (**11b***) (Scheme 6). In other words, although a complete chirality transfer from substrate to spirooxindole was observed, the same was not depicted in the formation of quinolone and *df*-oxindole scaffolds wherein reduction of the enantiomeric excess in the products was observed (Scheme 6). Therefore, further experiments needs to be designed and executed to unravel the influence of oxindole 1,6-enynes (**6**) on the stereogenic control over the diverse scaffolds formed.



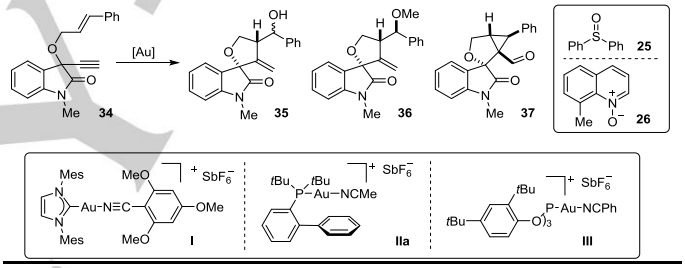
[a] Cat. **III**, DCM (0.1 M), rt. [b] Cat. **IIb**, DCM (0.1 M), rt. [c] MeOH (10 eq), Cat. **IIa**, DCE (0.1 M), 60 °C.

Scheme 6. Chirality transfer in gold(I)-catalyzed divergent scaffold synthesis.

Cycloisomerizations of oxindole derived 1,6-enyne with a terminal alkyne

After studying the role of substitutions on the olefin moiety of 1,6-enynes in guiding the gold(I)-catalyzed cycloisomerization reactions, we investigated the influence of terminal alkyne in enyne **34** on gold(I)-catalyzed divergent scaffold synthesis. In order to discover new reaction pathways leading to novel scaffolds, a reaction screening with different gold(I) catalysts as well as with different nucleophiles was carried out (Table 4).[29] In the absence of a nucleophile, and with gold(I) catalysts, **I** and **IIa**, enyne **34** yielded an inseparable mixture of products and trace amounts of spirooxindoles **35** (entry 1-2). Electrophilic phosphite-gold(I) catalyst **III** afforded the diastereomeric hydroxyl adducts (**35**) in 57% yield (dr = 1:1, entry 3). We anticipated that the products were formed by nucleophilic addition of a trace amount of water to a reaction intermediate. Indeed, when the same reaction was performed in the presence of 4 Å molecular sieves (4 Å MS), starting material (**34**) was fully recovered (entry 4).

Table 4. Nucleophile-guided gold(I)-catalyzed divergent scaffold synthesis with terminal alkyne substrate.



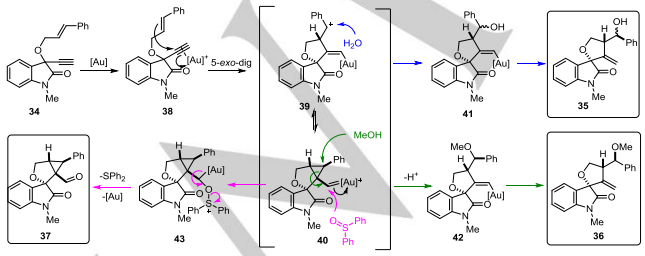
Entry[a]	[Au] (5 mol%)	Nu.(eq)	Yield (%)		
			35	**36**	**37**
1	**I**	-	trace[b]		
2	**IIa**	-	trace[b]		
3	**III**	-	57[c]		
4[d]	**III**	-	-[e]		
5	**I**	MeOH (20)		81	
6	**IIa**	MeOH (20)	-	72	
7	**III**	MeOH (20)		90	
8	**I**	**25** (1.2)	trace		Trace
9	**IIa**	**25** (1.2)	trace		16
10	**III**	**25** (1.2)	trace		21
11[d]	**III**	**25** (1.2)			52
12[f]	**I**	**26** (1.2)	[b]		trace
13[f]	**IIa**	**26** (1.2)	-[e]		
14[f]	**III**	**26** (1.2)	-[e]		

[a] Reaction condition: DCE (0.03 M), rt, overnight; [b] Complex mixture formation; [c] dr = 1:1; [d] Addition of 4 Å MS; [e] Starting material recovery; [f] 60 °C seal tube.

In order to efficiently trap the intermediate, MeOH was employed as nucleophile in the gold(I)-catalyzed cycloisomerization reaction. The NHC- or phosphine-gold(I) catalysts, **I** or **IIa**, delivered the methoxy adduct (**36**) in high yields (entry 5-6). The relative configuration of **36** was determined by single crystal X-ray structure analysis (Supporting information). The best yield of **36** (90%) was obtained employing phosphite-gold(I) catalyst (**III**, entry 7) in the cycloisomerization reaction.

We also examined sulfoxide (**19**) as oxidative nucleophile for gold(I) catalysed transformation of enyne **34**. Using NHC-gold(I) catalyst (**I**), only a trace amount of cyclopropyl spirooxindole (**37**) was observed (entry 8). Further reaction screening revealed that phosphite gold(I) complex **III** enhanced the yield of spirooxindole **37** to 21% (entry 10). Since hydroxylated adducts were always observed in the crude products, we tried to perform the reaction in anhydrous condition. Thus, in the presence of molecular sieves (4 Å), the desired product **37** was formed in 52% yield (entry 11, for single crystal X-ray structure analysis, see Supporting information). On the other hand, using *N*-oxide (**26**) as oxidative nucleophile in cycloisomerization reactions, either non-selective product formation was observed or starting material was recovered (entry 12-14).

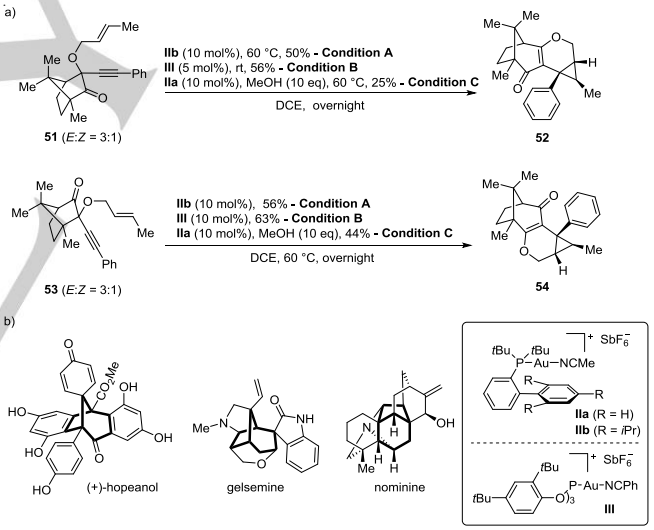
We assume that under gold(I) catalysis, the terminal alkyne substrate (**34**) follows a 5-*exo*-dig cyclization (Scheme 7), which is very different from the enyne substrates with aryl substituted alkyne (**6** and **7**, 6-*endo*-dig). Thus, gold(I) activated enyne (**38**) undergoes a 5-*exo*-dig cyclization to give spiro-intermediates (**39** and **40**). Trace amount of water may serve as nucleophile and add to the relatively stable benzylic cation in **39** forming adducts **41** which undergo protodeauration to form diastereomeric hydroxyl-*df*-oxindoles (**35**). With an excess of MeOH, the alcohol undergoes 1,4-addition to open up the cyclopropane of bicyclic gold carbene intermediate (**40**), giving vinyl gold intermediate (**42**). After protodeauration of **42**, the methoxy-*df*-oxindole (**36**) is formed.[30] It seems that, instead of 1,4-addition, sulfoxide (**19**) proceeds *via* a 1,2-addition to the bicyclic gold carbene intermediate (**40**), which sequentially oxidizes the gold carbene to the carbonyl moiety and thus forming a cyclopropane-fused tetracyclic aldehydic spirooxindole (**37**).[31]



Scheme 7. Proposed reaction mechanisms of nucleophile guided gold(I) catalysed cycloisomerizations of terminal alkyne substrate.

Replacing the privileged-ring-system: Cycloisomerization of camphor-ring based 1,6-enynes

In the light of successful access to structurally intriguing scaffolds from oxindole based 1,6-enynes described above, another naturally occurring ring-system, *i.e.* the camphor framework was introduced into enyne system to investigate the LDS strategy.[32] The camphor based 1,6-enyne was prepared by means of lithium phenylacetylide addition to the carbonyl group of camphorquinone and followed by *O*-allylation of newly generated propargyl alcohol (see the Supporting information). By employing the optimal conditions developed for the LDS in the crotylated 1,6-enyne system, we observed that the ring expansion products (**52** and **54**) were selectively generated from camphor based crotylated 1,6-enynes (**51** and **53**, Scheme 8). The bicyclic [3.2.1] products (**52**) can be prepared in 50% yield from the substrate **51** by using sterically demanding phosphine gold(I) catalyst **IIb** at 60 °C (condition A, Scheme 8a). A better yield was obtained when phosphite-gold(I) complex **III** was used as catalyst at room temperature (56%, condition B, Scheme 8a). Having MeOH as external nucleophile could not trap the gold carbene cyclopropane intermediate to follow the *O*-migration reaction and only the ring expansion product (**52**) was obtained in low yield (condition C, Scheme 8a).



Scheme 8. a) Cationic gold(I) catalyzed bicyclic [3.2.1] system formation via acyl migration; and b) Natural products containing the bicyclic [3.2.1] system.

The camphor-based-crotylated 1,6-enyne **53** did not undergo enyne cycloisomerization at room temperature. At higher reaction temperature, *i.e.* at 60 °C, the desired ring expansion product (**54**) was obtained in 56% yield using gold(I) catalyst **IIb** (condition A, Scheme 8a). The phosphite gold(I) catalyst **III** gave afforded higher yield for **54** (conditions B, Scheme 8a). Having MeOH again as external nucleophile with gold(I)-complex **II** provided inconsequential and led to form **54** in moderate yield (conditions A and C, Scheme 8a). The relative configurations of bicyclic [3.2.1] products (**52** and **54**) were unambiguously determined by 2D NMR analysis, i.e. by COSY,

HSQC, HMBC, and NOESY (see supporting information). Apparently, the pinacol type acyl migration is the major pathway for releasing the intrinsic ring strain between the camphor backbone and the gold catalysts to generate enantiomerically pure bicyclic [3.2.1] products (**52** and **54**). The bicyclic [3.2.1] core-structure is frequently found in many natural products, such as (+)-hopeanol,[33] geisemine,[34] and nominine[35] (Scheme 8b), and therefore small molecules based on this molecular scaffold may offer interesting bio-modulating properties.

Conclusions

In summary, the ligand-directed divergent synthesis strategy to deliver distinct molecular scaffolds was explored using gold(I)-catalyzed cycloisomerization reactions of 1,6-enynes. The role and influence of various substitutions on the olefin moiety of the enynes as well as that of external nucleophiles in directing and guiding different reaction pathways from common reactive intermediates was investigated. Overall, about 10 different gold(I)-catalysed transformations were identified that transformed the oxindole-based 1,6-enyne substrates into distinct scaffolds. In addition, the naturally occurring bicyclic [3.2.1] system was constructed from camphor based 1,6-enynes employing a gold(I)-catalyzed pinacol type acyl group migration reaction. The LDS strategy has substantial potential for the effective synthesis of diverse and complex chemotypes and will find further applications in organic synthesis of complex small molecules.

Experimental Section

General procedure for gold(I)-catalyzed cycloisomerization reactions
At 0 °C, to a mixture of 1,6-enyne (**6**/**7**, 0.1 mmol) and corresponding gold catalyst (5 µmol) was added dry DCM (1.0 ml) under $Ar_{(g)}$ atmosphere. After warming to room temperature, the reaction mixture was stirred overnight and then passed through a short pad of silica gel (Et_2O as eluent). The resulting solution was concentrated under reduced pressure, followed by silica gel column chromatography (EtOAc / Petroleum ether as eluent) to obtain the desired product.

General procedure for nucleophile addition in gold(I)-catalyzed cycloisomerization ractions
To a mixture of 1,6-enyne (**6**/**7**, 0.15 mmol), gold(I) catalyst (**IIa**, 5.8 mg, 7.5 µmol), and corresponding nucleophile, *i.e.* MeOH (61 µL, 1.51 mmol), sulfoxide **25** [945-51-7] (61 mg, 0.30 mmol), or *N*-oxide **10** [4053-38-7] (27 mg, 0.17 mmol), in a pressure tube equipped with a stirring bar was added DCE (1.5 mL) and the mixture was stirred at 60 °C until TLC showed full conversion of the starting material. After cooling to room temperature, the reaction mixture was passed through a short pad of silica gel (Et_2O as eluent). The resulting solution was concentrated under reduced pressure, followed by silica gel column chromatography (EtOAc / Petroleum ether as eluent) to obtain the desired product.

General procedure for ligand and nucleophile variation approach with terminal alkyne substrates
To a mixture of 1,6-enyne (**34**, 10 mg, 0.03 mmol), gold(I) catalyst (1.7 µmol), and corresponding nucleophile, *i.e.* dry MeOH (27 µL, 0.66 mmol), diphenyl sulfoxide **25** [945-51-7] (8 mg, 0.04 mmol), or *N*-oxide **26** [4053-38-7] (6 mg, 0.04 mmol), was added dry DCM (1.0 mL).* The mixture was stirred at room temperature overnight. Resulting reaction mixture was passed through a short pad of silica gel (Et_2O as eluent). The filtrate was concentrated under reduced pressure, followed by silica gel column chromatography (EtOAc / Petroleum ether as eluents) to obtain desired product. In some cases, it is required to add 4 Å MS (10 mg) to reaction mixture (see Table 4 and Supporting information).

X-ray crystallography
CCDC 1448387 (**9f**), CCDC 1577705 (**15**), CCDC 1577695 (**16**), CCDC 1577715 (**17**), CCDC 1577690 (**18**), CCDC 1577276 (**36**), and CCDC 1577691 (**37**) contain crystallographic data for this paper. These data can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: gold(I) catalysis • enynes • heterocycles • divergent synthesis • scaffold diversity

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A ligand-directed divergent scaffold synthesis was explored by varying the ligands in the gold(I) catalysts and the nucleophiles in the cycloisomerization reactions of oxindole based 1,6-enynes. The strategy afforded a number of distinct and structurally complex molecular scaffolds.

Key topic: Gold(I) Catalysis

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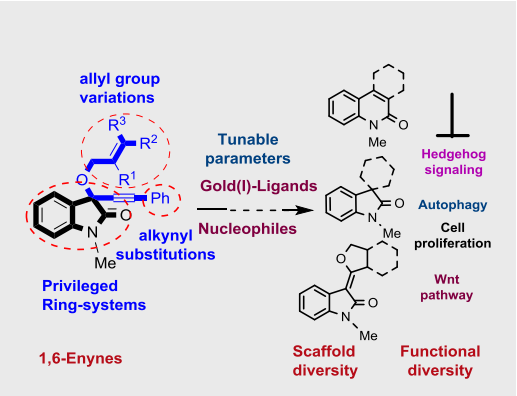

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Gold(I)-catalyzed and Nucleophile-guided Ligand-directed Divergent Synthesis