# Gold and Carbene Relay Catalytic Enantioselective Cycloisomerization/Cyclization Reactions of Ynamides and Enals

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***Abstract:*** *The combined use of gold as transition metal catalyst and N-heterocyclic carbene (NHC) as organic catalyst in the same solution for relay catalytic reactions was disclosed. The ynamide substrate was activated by gold catalyst to form unsaturated ketimine intermediate that subsequently reacted with the enals (via azolium enolate intermediate generated with NHC) effectively to form bicyclic lactam products with excellent diastereo- and enantio-selectivities. The gold and NHC coordination and dissociation can be dynamic and tunable events, and thus allow the co-existence of both active metal and carbene organic catalysts in appreciable concentrations, for the dual catalytic reaction to proceed.*

Transition metal catalysts have found enormous success in activating a large set of chemical bonds in organic synthesis. In recent decades, simple organic molecules have also emerged as effective catalysts of choice. It has been accepted that merging transition metals and organic catalysts shall expand the horizons of organic synthesis by providing new modes of activations or shorter synthetic routes.[1] Success in this direction mainly came from organic catalysts that do not typically show tight coordinations with transition metals.[2] A relatively well-studied system involves a transition metal catalyst (such as gold, palladium, iridium, ruthenium) with a chiral amine[3] or phosphoric acid[4] catalyst. N-heterocyclic carbenes (NHCs) as organic catalysts exhibit unique catalytic modes with many possible reaction pathways.[5] However, the

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combination of NHCs as organic catalysts with transition metal catalysts are much less developed.[6,7] This is in part due to the fact that the NHC can behave as a strong coordinating ligand for transition metals.[6] Elegant while still limited success mainly involves the incorporation of π-allyl-palladium intermediate with NHC organic catalysis, as reported by Liu, Scheidt, Glorius, and Ohmiya (Figure 1 A).[7]
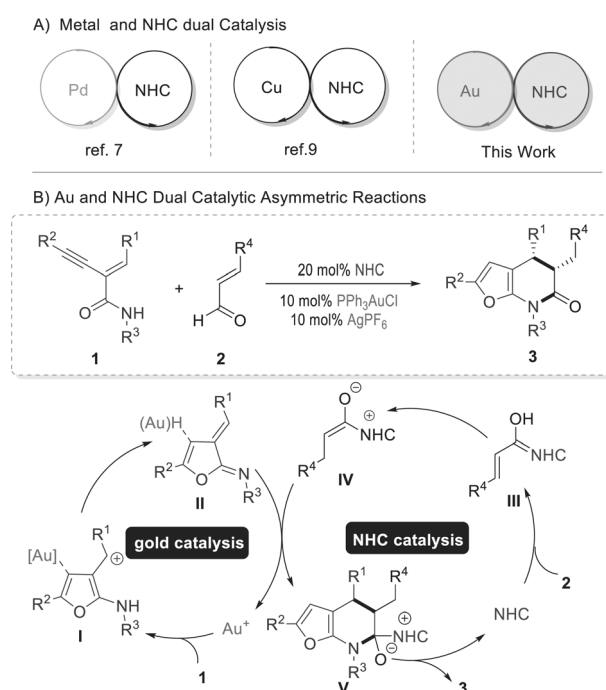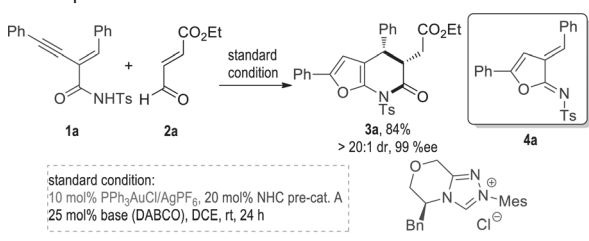


**Figure 1.** NHC organic catalysis and transition metal catalysis.

Our laboratory is interested in the development of new activations and reactions by combination of the NHC organic catalyst with a second catalyst.[8] In 2014, we disclosed that the copper catalyst and NHC organic catalyst could be merged in the same solution to mediate a three-component reaction (Figure 1 A).[9] Herein, we disclose that the gold catalyst is compatible with NHC organic catalysts for highly enantioselective cycloisomerization/azadiene Diels–Alder reactions (Figure 1 B). In this reaction, Au-catalyzed the activation of ynamide (**1a**)[10] to generate adduct **I** that further isomerize to α,β-unsaturated *N*-sulfonyl ketimine[11] (**II**) as a key intermediate. Concurrently, NHC converts an enal substrate (**2**) to form Breslow intermedaite **III** that undergo a proton transfer process to form an azolium enolate intermediate (**IV**). Reaction of intermediates **II** and **IV** affords bicyclic lactam

product **3** with an excellent yield and er value, with both Au and NHC catalysts regenerated. Product **3** is not formed when either Au or NHC was not present. Built on the existing rich chemistry of Au[12] and NHC,[13] we expect this study to encourage further development of a sizeable set of new synthetic strategies that are not readily available with single-catalyst approaches.

We chose ynamide **1a** and enal **2a** as the model substrates to test our hypothesis and search for suitable dual catalytic conditions (Table 1). An optimal condition involves 10 mol %

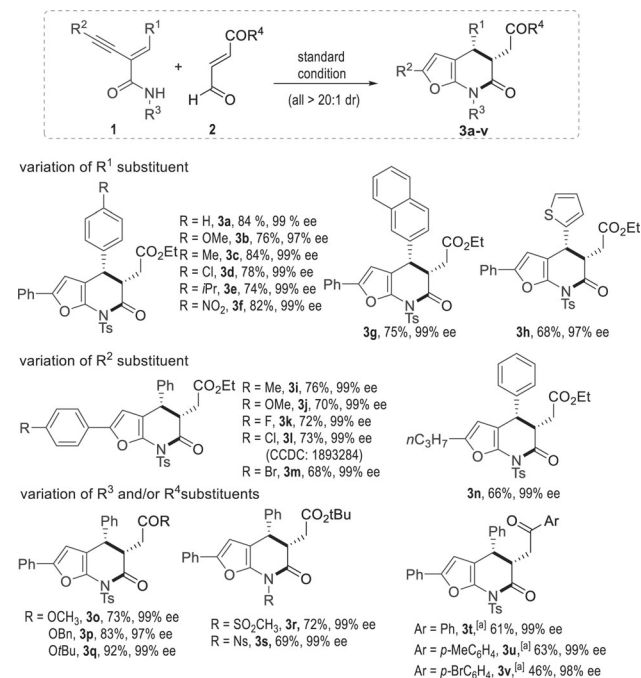**Table 1:** Optimization of the reaction conditions.[a]



| Entry | Variation from standard conditions | Yield (3a) [%][b] | Yield (4a) [%][b] | 3a dr, ee [%] |
|---|---|---|---|---|
| 1 | none | 84 | – | > 20:1, 99 |
| 2 | no PPh₃AuCl/AgPF₆ | 0 | none | – |
| 3 | no AgPF₆ | 0 | none | – |
| 4 | no PPh₃AuCl | 0 | none | – |
| 5 | no NHC | 0 | 93 | - |
| 6 | 10 mol % instead of 20 mol % NHC | trace | 89 | – |
| 7 | DBU as base | 63 | – | 12:1, 96 |
| 8 | Et₃N as base | 67 | – | 13:1, 91 |
| 9 | DMAP as base | 72 | – | > 20:1, 99 |
| 10 | Cs₂CO₃ as base | 60 | – | 9:1, 96 |

[a] Reactions were conducted on a 0.1 mmol scale of **1a**. [b] Isolated yield of **3a**.

PPh₃AuCl/AgPF₆ as the effective gold catalyst, triazolium **A** as the NHC pre-catalyst, DABCO as the base, and dichloroethane (DCE) as the solvent at room temperature (Table 1, entry 1). Under this standard condition, the desired bicyclic lactam product **3a** was obtained in 84 % yield, > 20:1 dr and 99 % *ee*. When PPh₃AuCl/AgPF₆ was not used, **3a** was not obtained (entry 2). As extensively documented in gold catalysis, the use of AgPF₆ is essential to release the active gold catalyst from PPh₃AuCl. Thus, when AgPF₆ was not present, **3a** could not be formed (entry 3). The presence of PPh₃AuCl is crucial for the formation of **3a**, and AgPF₆ alone did not have the ability to activate the alkyne substrate **1a** (entry 4). When triazolium NHC pre-catalyst **A** was not added (to activate the enal substrate **2a**), the lactam product **3a** was not obtained either (entry 5). When the loading of NHC was decreased from 20 to 10 mol %, lactam **3a** was formed in only trace amount (entry 6). Under these conditions (entries 5,6), **4a** was formed through Au-mediated activation of alkyne substrate **1a**. These observations (entries 1–6) clearly indicate that both Au and NHC catalysts

are crucial for the formation of product **3a**. The dual catalytic reaction proceeded well when other bases (entries 7–10) were used.
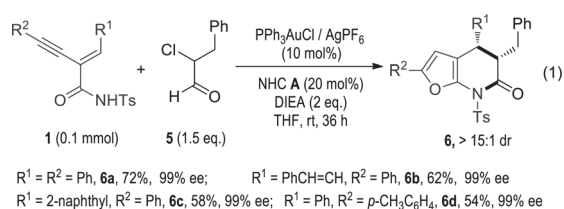
With the optimum condition in hand, the substrate scope was explored (Scheme 1). We first evaluated ynamide substrates by using enal **2a** as the other reactant to afford product **3a–n**. The substituent connected to the alkene terminal



**Scheme 1.** Scope of the reaction. The reaction conditions are as those in Table 1, entry 1, unless otherwise noted. [a] CHCl₃ was used instead of DCE.
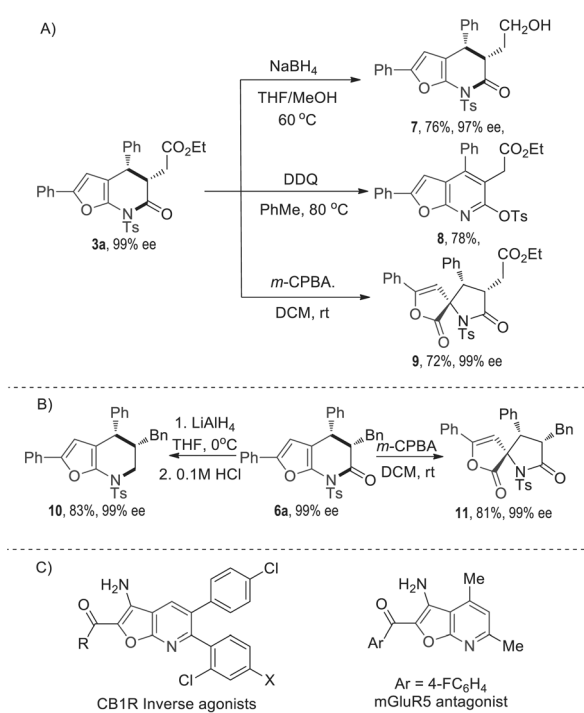
carbon (R¹) of substrate **1** can be a phenyl unit with different substitutions (**3b–f**). The R¹ substituent can be a naphthalene (**3g**) or thiophene (**3h**) group. The substituents attached to the alkyne moiety of substrate **1** can be aryl (**3i–m**) or alkyl (**3n**) functional groups. In all these cases (**3a–n**), the reaction products were obtained with good to excellent yields, exceptional diastereo- and enantioselectivities. Changing ethyl ester group of substrate **2** to methyl, benzyl, and *tert*-butyl esters were tolerated well (**3o–q**). Notably, the use of enal substrate with a β-*tert*-butyl ester substituent afforded the corresponding products consistently with higher yields (for example, **3q**, 92 % yield, 99 % *ee*). The N-substituent of **1** could be changed from Ts to Ns (*p*-nitrobenzenesulfonyl) or Ms (SO₂CH₃), with little influence on the reaction yields or selectivities (**3r**, **3s**). Finally, the ester substituent on enal β-carbon could be replaced with a ketone group (**3t–v**). The absolute configuration of **3l** was unambiguously confirmed by single-crystal X-ray diffraction analysis (see Supporting Information).

The versatility of the Au and NHC dual catalytic approach was further demonstrated by using α-chloro aldehyde **5** as the substrate to replace enals **2** [Eq. (1)]. The standard condition (Table 1, entry 1) was only slightly modified to accommodate this substrate with an alternative pathway for the generation

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Equation (1):

1 (0.1 mmol) + 5 (1.5 eq.) → PPh₃AuCl / AgPF₆ (10 mol%), NHC **A** (20 mol%), DIEA (2 eq.), THF, rt, 36 h → **6**, > 15:1 dr

R¹ = R² = Ph, **6a**, 72%, 99% ee;     R¹ = PhCH=CH, R² = Ph, **6b**, 62%, 99% ee
R¹ = 2-naphthyl, R² = Ph, **6c**, 58%, 99% ee;    R¹ = Ph, R² = *p*-CH₃C₆H₄, **6d**, 54%, 99% ee

of azolium enolate intermediate (**IV**, Figure 1 b). All the products (**6a–d**) were obtained with acceptable yields, > 15:1 dr and 99% *ee* values.

The products obtained in our approach contain a furan ring fused with a six-membered lactam and could be easily elaborated in different ways. Herein, we demonstrate several transformations using catalytic reaction products **3a** or **6a** as the substrate (Scheme 2). The ester unit of **3a** could be
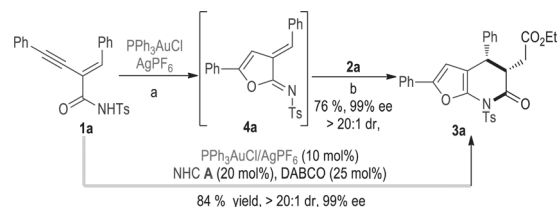


**Scheme 2.** Synthetic Transformations of Product **3a** and **6a**.

reduced with NaBH₄ to give the corresponding alcohol **7** in 76% yield, with the enantiomeric excess of the product remained. Compound **3a** could also undergo an oxidative aromatization process to form furo[2,3-b]pyridine **8** in 78% yield. Furo[2,3-b]pyridine has recently received extensive attention as a key pharmacophore of several potential drug candidates[14] (Scheme 2 C). Interestingly, treatment of bicyclic δ-lactam (**3a**) with *meta*-chloroperoxybenzoic acid (*m*-CPBA) led to an unexpected oxidative rearrangement to give a spirocyclic compound **9** that are key intermediates for the synthesis of complex marine alkaloid.[15] The catalytic reaction product **6a** could also be reduced to form furo[2,3-b]tetrahydropyridines **10** in 83% yield with 99% *ee*. Similar oxidative rearrangement of **6a** could also give spirocyclic

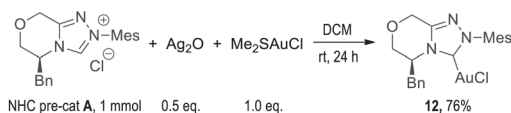adduct **11** in good yield without erosion on the optical purity (Scheme 2 B).

To understand the reaction pathways, we carried out the reaction in a stepwise manner (Scheme 3). α,β-Unsaturated *N*-sulfonyl imine **4a** was afforded as the only product from ynamide **1a** under the catalysis of PPh₃AuCl/AgPF₆
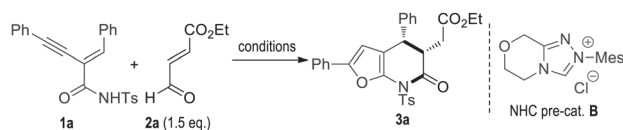


**Scheme 3.** Control reaction. a) PPh₃AuCl/AgPF₆(10 mol%), 1 h. b) NHC **A** (20 mol%), DABCO (25 mol%), 20 h.

(10 mol%) without enal **2a** or NHC **A** (monitored by ¹H NMR). Subsequent addition of enal **2a** and NHC **A** (20 mol%) into the reaction system could give the product **3a** in 76% yield and 99% *ee*. The similar results from the stepwise reaction (Scheme 3) with the reaction (Table 1, entry 1) suggest that the reaction proceed through a relay catalytic pathway. As a technical note, some of the α,β-unsaturated *N*-sulfonyl imine intermediates are not stable (for example, imine generated from **6b**) and cannot give the desired final products from a stepwise reaction. Our relay catalytic approach can efficiently avoid decomposition of the imine intermediates and give the desired products in good to excellent yields and optical purities.

Control experiments were carried out to gain more insights into the reaction mechanism (Table 2). Reaction of NHC-precursor **A** with 0.5 equiv Ag₂O and 1.0 equiv Me₂SAuCl in DCM gave complex **12** (Table 2 A). Product **3a** was not obtained (Table 2 B, entries 1 and 2) when complex **12** was used as the single metal-catalyst with or without the presence of AgPF₆, which was consistent with the nature of the strong coordination between gold and NHC in solution. To our surprise, the combination of 10 mol% of gold-catalyst (generated from **12**/AgPF₆) and 10 mol% of NHC-catalyst (generated from **A**/DABCO) as a dual catalytic system was still ineffective (generated **4a** in 85% yield, Table 2 B, entry 3). This is attributed to the fact that the newly generated free carbene can coordinate with the activated gold center to form a bis(carbene) gold species, which was detected in situ by the HRMS analysis (see Supporting Information P8).[16] Accordingly, improving the loading of **A** to 20 mol% (two equiv to **12**) gave rise to **3a** in 76% yield and 99% *ee* (Table 2 B, entry 4). Alternatively, addition of 10 mol% of PPh₃ into the reaction mixture of entry 2 lead to **3a** in 58% yield and 99% *ee*, suggesting the release of NHC catalyst owing to the competing ligation between PPh₃ and NHC in the reaction media (Table 2 B, entry 5). These results indicated that the second carbene ligation onto the gold(I) sphere is relatively weak and can readily undergo dissociation and coordination in the gold/carbenes dual catalytic system, as further supported by the following experiment (Table 2 B, entry 6). When an achiral NHC pre-catalyst (**B**) was com-

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**Table 2:** Mechanistic Studies.

A) synthesis of **NHC-Au-Cl** gold catalyst **12**



NHC pre-cat **A**, 1 mmol   0.5 eq.   1.0 eq.      **12**, 76%

B) control experiments to probe reaction mechanism



| Entry | Conditions | 3a [%] | 4a [%] | 3a ee [%] |
|-------|-----------|--------|--------|-----------|
| 1 | **12** (10 mol%) | 0 | 0 | – |
| 2 | **12**/AgPF$_6$ (10 mol%) | 0 | 87 | – |
| 3 | **12**/AgPF$_6$ (10 mol%), NHC **A** (10 mol%) DABCO (12 mol%) | trace | 85 | – |
| 4 | **12**/AgPF$_6$ (10 mol%), NHC **A** is 20 mol%, DABCO (25 mol%) | 76 | – | 99 |
| 5 | **12**/AgPF$_6$ (10 mol%), NHC **A** (10 mol%) PPh$_3$ (10 mol%), DABCO (12 mol%) | 58 | – | 99 |
| 6 | **12**/AgPF$_6$ (10 mol%), NHC **B** (20 mol%), DABCO (25 mol%) | 68 | – | 43 |

bined with gold complex **12** containing a chiral NHC ligand, the reaction product **3a** could be obtained with moderate enantioselectivity (see Supporting Information). This enantioselectivity indicated that the aldehyde substrate **2a** was likely activated by both achiral carbene catalyst (from **B**) and chiral NHC catalyst (from the NHC-gold complex **12**).

In summary, we have developed a relay catalytic strategy involving gold and NHC catalysts for efficient synthesis of bicyclic lactam products. In our approach, gold as transition metal catalyst and NHC as organic catalyst can be compatible in the same solution for relay asymmetric catalysis. We expect this study to encourage further explorations in dual metal and organic catalytic activations and reactions. Further mechanistic studies, reaction development, and synthetic applications of this approach are in progress in our laboratory.

## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** bicyclic lactams · gold catalyst · N-heterocyclic carbenes · relay catalysis

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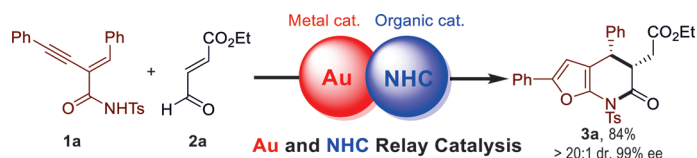
## Communications

**Relay Catalysis**

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Gold and Carbene Relay Catalytic
Enantioselective Cycloisomerization/
Cyclization Reactions of Ynamides and
Enals

**The combination of gold catalyst** and N-heterocyclic carbene (NHC) in the same solution for relay reactions was disclosed. The ynamide substrate was activated by gold catalyst to form an intermediate that subsequently reacted with the enals to form bicyclic δ-lactam products with excellent diastereo- and enantio-selectivities.