# The Combination of Relay and Cooperative Catalysis with a Gold/Palladium/Brønsted Acid Ternary System for the Cascade Hydroamination/Allylic Alkylation Reaction

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**Abstract:** The combination of relay and cooperative catalysis with a gold/palladium/Brønsted acid ternary system renders a cascade hydroamination/allylic alkylation reaction to provide an unprecedented entry to pyrrolidine derivatives in high yields.

**Keywords:** allylic alkylation; Brønsted acids; cooperative catalysis; hydroamination; metal/organocatalyst ternary system; pyrrolidine derivatives; relay catalysis

The capability of nature to produce structurally complex organic molecules from simple substrates relies highly on the cascade reaction by using disciplinarily diverse biocatalysts, which operate in cooperative or relay manner.<sup>[1]</sup> In addition to these events occurred *in vivo*, the conceptually similar strategy can principally be realized *in vitro* upon reasonable tuning of multiple catalyst systems. As such, unprecedented cascade reactions would be created for the generation of structurally complex products from relatively simple starting materials. In the last decades, homogeneous catalysis has been dominantly dependent on single catalyst species.<sup>[2]</sup> Although some successful attempts have been performed on the development of organic/ metallic binary catalysis<sup>[3–5]</sup> or organogold dual metal catalysis,<sup>[6,7]</sup> cascade reactions by heterometallic/organíc multiple catalyst systems, which represent the mimic of variants occurring in nature by using disciplinarily diverse biocatalysts, remain elusive. As a proof of concept, we herein report a gold/palladium/Brønsted acid ternary system, which works in relay and cooperative manner, offering an unprecedented access to pyrrolidine derivatives.

Secondary amine-bridged enynes of type **1** are principally able to undergo a hydroamination to give an *N*-allylic enamine intermediate **II** under the catalysis of gold complexes (Scheme 1).<sup>[8]</sup> Subsequently, the *N*-allylic enamine **II** might participate in an allylic alkylation under the cooperative catalysis of a palladium complex and a Brønsted acid *via* an intermediate **III** as demonstrated by previous elegant work.<sup>[9]</sup> As such, this "relay-cooperative catalysis" would enable a cas-



Scheme 1. The proposed relay-cooperative catalysis.

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Table 1. Recruiting the optimal catalyst system and conditions.<sup>[a]</sup>



<sup>[a]</sup> Unless indicated otherwise, a mixture of **1** (0.1 mmol), a gold complex (5 mol%), palladium (5 mol%), phosphine ligand (10 mol%), and Brønsted acid (5 mol%) in toluene (1.0 mL) was stirred at 70 °C under argon.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> 15 mol% **L1** was used.

<sup>[d]</sup> The Ph<sub>3</sub>PAuOTf was *in situ* generated from 5 mol% of Ph<sub>3</sub>PAuCl and 5 mol% of AgOTf.

[e] 5 mol% of **L1** was used.

<sup>[f]</sup> 15 mol% of **L1** was used.

<sup>[g]</sup> 7.5 mol% of Brønsted acid **3** was used.

cade hydroamination/allylic alkylation reaction, offering a new entry to dihydropyrroles **2**.

The validation of the proposed strategy began with a reaction of diethyl 2-(allylamino)-2-(4-phenylbut-3ynyl)malonate (**1a**) in the presence of a combined catalyst system of  $5 \mod \text{M} \operatorname{Pd}(\operatorname{PPh}_3)_4$ ,  $5 \mod \text{M} \operatorname{Ph}_3\operatorname{PAuNTf}_2^{[10]}$  and  $5 \mod \text{M}$  of binol-derived racemic phosphoric acid **3** at 70 °C in toluene (Table 1, entry 1). However, the desired product **2a** was isolated in a poor yield (9%). Encouragingly, when Pd(dba)<sub>2</sub> was used as a precatalyst, the variation of phosphine ligands was able to improve the reaction efficiency. Thus, the presence of 10 mol% of triphenylphosphine rendered the reaction to give a 25% yield (entry 2). A further improved yield could be achieved upon exploiting triphenyl phosphite as a ligand (entry 3, 63% yield). Among the Buchwald ligands<sup>[11]</sup> screened (entries 4–6), the electronically rich and sterically bulky phosphine **L1**<sup>[11a]</sup> (Figure 1) turned out to be best ligand for the reaction (entry 4). The comparison of other palladium sources with Pd(dba)<sub>2</sub> found that Pd(dba)<sub>2</sub> was the precatalyst of choice (entries 4, 7, and 8). Although palladium acetate offered a comparable yield with Pd(dba)<sub>2</sub>, a rela-





F	ξ <sup>1</sup>	$5 \text{ mol}^{\circ}$ 5 mol^{\circ} R^2 10 mc 7.5 m	% Ph <sub>3</sub> PAuNTf <sub>2</sub> % Pd(dba) <sub>2</sub> il% <b>L1</b> ol% <b>3</b>		
		toluen	e, 70 °C, Ar		$R^2$
EtO <sub>2</sub> C <sup>´</sup> CO <sub>2</sub> Et R'					
	1				2
Entry	2	$\mathbf{R}^1$	$\mathbb{R}^2$	Time [h]	Yield [%] <sup>[b]</sup>
1	2b	$4-FC_6H_4$	Н	3	63
2	<b>2c</b>	$4-ClC_6H_4$	Н	3	75
3	2d	$4 - PhC_6H_4$	Н	3	80
4	2e	$4-t-BuC_6H_4$	Н	3	72
5	2f	$4-CF_3C_6H_4$	Н	3	60
6	2g	3-MeOC <sub>6</sub> H <sub>4</sub>	Н	3	81
7	2ĥ	2-naphthyl	Н	3	76
8	2i	$3,5-F_2C_6H_3$	Н	3	53
9	2j	Ph	Ph	12	71
10	2k	Ph	$4 - MeC_6H_4$	12	77
11	21	Ph	4-MeOC <sub>6</sub> H <sub>4</sub>	12	79

Table 2. Generality of the reaction.<sup>[a]</sup>

 <sup>[a]</sup> Unless indicated otherwise, a mixture of 1 (0.1 mmol), Ph<sub>3</sub>PAuNTf<sub>2</sub> (5 mol%), Pd(dba)<sub>2</sub> (5 mol%), L1 (10 mol%), and 3 (7.5 mol%) in toluene (1.0 mL) was stirred at 70 °C under argon.

<sup>[b]</sup> Isolated yield.

tively larger amount of phosphine ligands was required, probably due to in situ generation of palladium(0) species. The examination of gold(I) complexes<sup>[10]</sup> indicated that the more cationic gold complex provided a more complete reaction (entries 9 and 10 vs. 4) and we found that  $Ph_3PAuNTf_2$  turned out to be the best catalyst for the hydroamination step. The evaluation of Brønsted acids led to a conclusion that the acidity<sup>[9b,12]</sup> has a considerable effect on the reaction. Seemingly, the more acidic Brønsted acid delivered a cleaner reaction (entries 11-13) while the phosphoric acid gave the best results (entry 4). The highest yield could be achieved when the ratio of L1 to  $Pd(dba)_2$  was 2/1 and the loading of 3 was tuned to 7.5 mol% (entries 4 and 14–16). However, in the absence of the phosphoric acid, the reaction proceeded incompletely to give the desired product in a poor yield (entry 17), indicating that the palladium and Brønsted acid really operate cooperatively on the allylic alkyltion.<sup>[9]</sup>

The generality of the protocol was next explored (Table 2). A variety of secondary amine-bridged enynes **1** was probed as substrates. The introduction of a substituent to the phenylacetylene moiety of **1** led to a smooth cascade reaction under the relay-co-operative catalysis while the electronic feature exerts some impact on the reaction performance. Basically, the presence of a highly electron-withdrawing substituent resulted in a moderate yield (entries 1, 5 and 8). In contrast, much higher yields were delivered



**Scheme 2.** The relay and cooperative catalysis with *N*-allyl-5-phenylpent-4-yn-1-amine.

with the substrates 1 bearing either electronically less deficient, neutral or rich aryl substituents bonded to the acetylene subunit (entries 2–4 and 6). The installation of a substituent at the olefin moiety was also tolerated, giving the desired products in high yields (entries 9–11).

However, the extension of the optimal conditions to *N*-allyl-5-phenylpent-4-yn-1-amine (**1m**), which has no substituents at the  $\alpha$ -carbon to amine, gave the desired product in a low yield.<sup>[13]</sup> Because the hydroamination step proceeded smoothly under the catalysis of Ph<sub>3</sub>PAuNTf<sub>2</sub>, we envisioned that the key problem might exist in the allylic alkylation. Thus, a re-evaluation of palladium catalysts<sup>[14]</sup> was performed and we found that Pd(PPh<sub>3</sub>)<sub>4</sub> was the best co-catalyst to enable the whole sequential reaction to give the final product in 80% yield (Scheme 2).

A series of control experiments was conducted to gain insight into the mechanism of the transformation. No reaction occurred when the acid 3 was used alone as the catalyst [Scheme 3, Eq. (1)]. In the absence of  $Ph_3PAuNTf_2$  and **3**, two compounds  $D_1$  and  $D_2$  were afforded, but no desired product 2d was observed [Eq. (2)]. An N-allylic enamine IId was isolated in a moderate yield (55%) when 1d was treated with  $Ph_3PAuNTf_2$  (5 mol%) in toluene at 70°C for less than 10 min [Eq. (3)]. A subsequent treatment of the intermediate IId with  $Pd(dba)_2$  (5 mol%), L1 (10 mol%), and **3** (7.5 mol%) gave **2d** in 62% yield at 70°C for 3 h [Eq. (4)].<sup>[15]</sup> On the contrary, without the Brønsted acid 3 only a very low yield (11%) of 2a was obtained (Table 1, entry 17), which indicated that the Brønsted acid 3 was necessary to facilitate the allylic alkylation step. These results revealed that the relay catalytic transformation really proceeded starting with the gold(I)-catalyzed hydroamination while Pd(0) and the Brønsted acid catalyzed the conversion of *N*-allylic enamine **II** into the pyrrolidines **2** in a cooperative manner.

In summary, we have developed a combination of the relay and cooperative catalysis with a gold/palladium/Brønsted acid ternary system enabling the secondary amine-bridged enynes to undergo cascade hydroamination and allylic alkylation reactions, providing an unprecedented entry to pyrrolidine derivatives in high yields. In this cascade reaction, the gold complex serves a catalyst responsible for the hydroamination



Scheme 3. Experimental evidence for the proposed mechanism.

while Brønsted acid and palladium cooperatively catalyze the allylic alkylation. This example might open a window for the future development of heterometallic/organo multiple catalyst systems. The investigations to reach this goal are now undergoing in our group.

# **Experimental Section**

#### General Procedure for the Cascade Hydroamination/ Allylic Alkylation Reaction

**Procedure 1:** A solution of **1** (0.1 mmol) in toluene (1.0 mL) was added to a mixture of Ph<sub>3</sub>PAuNTf<sub>2</sub> (5 mol%), Pd(dba)<sub>2</sub> (5 mol%), **L1** (10 mol%), and **3** (7.5 mol%) under argon. The resultant reaction solution was stirred at 70 °C for 3 or 12 h. Then, the reaction mixture was directly subjected to a flash column chromatography on silica gel (eluent: petroleum ether:ethyl acetate=15:1 to 10:1) to yield pure products **2a–2l**.

**Procedure 2:** A solution of **1m** (0.1 mmol) in toluene (1.0 mL) was added to a mixture of  $Ph_3PAuNTf_2$  (5 mol%),  $Pd(PPh_3)_4$  (5 mol%), and **3** (2.5 mol%) under argon. The resultant reaction solution was stirred at 70 °C for 8 h. Then, the reaction mixture was directly subjected to a flash column chromatography on silica gel (eluent: petroleum

ether:ethyl acetate: $Et_3N = 200:10:1$ ) to yield pure product **2m.** 

#### **Supporting Information**

Experimental details and characterization data of new compounds are given in the Supporting Information.

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- [13] A 32% yield was obtained after the reaction had proceeded for 3 h under the optimal conditions.
- [14] Variation of the combined catalysts and conditions revealed the following: (i) PPh<sub>3</sub>AuNTf<sub>2</sub> (5 mol%),

Pd(OAc)<sub>2</sub> (5 mol%), **L1** (15 mol%), **3** (7.5 mol%), toluene (1.0 mL), 70 °C, 5 h, yield: 43%; (ii) PPh<sub>3</sub>AuNTf<sub>2</sub> (5 mol%), Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> (5 mol%), **L1** (15 mol%), **3** (7.5 mol%), toluene (1.0 mL), 70 °C, 3 h, yield: 28%; (iii) PPh<sub>3</sub>AuNTf<sub>2</sub> (5 mol%), Pd(OAc)<sub>2</sub> (5 mol%), PPh<sub>3</sub>

(15 mol%), 3 (5 mol%), toluene (1.0 mL), 70 °C , 6 h, yield: 68%.

[15] The experiment details are described in the Supporting Information.