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Highly Enantioselective Relay Catalysis in the Three-Component Reaction for Direct Construction of Structurally Complex Heterocycles

Chao Wang, Zhi-Yong Han, Hong-Wen Luo, and Liu-Zhu Gong*

Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026, China

gonglz@ustc.edu.cn

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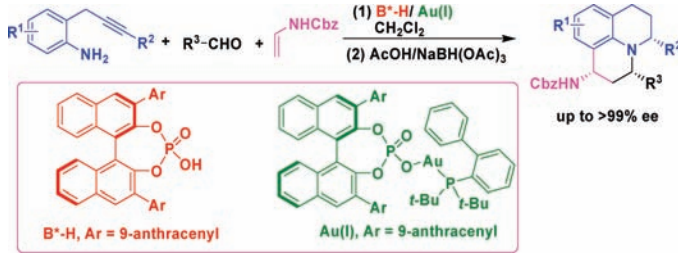
ABSTRACT



A highly enantioselective three-component cascade reaction, consisting of an enantioselective [4+2] cycloaddition reaction catalyzed by chiral phosphoric acid and a subsequent catalytic intramolecular hydroamination by gold(I) complex, provides a unique method to access structurally diverse julolidine derivatives in high optical purity.

Conventional wisdom implies that asymmetric reactions known so far are dominantly mediated by a single type of catalyst such as either a metal-based or an organocatalyst.[1] The organic/metallic binary catalyst systems that are comprised of two fundamentally different catalysts that operate cooperatively or sequentially in the same reaction solution, now known as cooperative catalysis and relay catalysis (or cascade catalysis), hold great potential in the creation of new transformations where each type of catalyst failed to afford alone.[2] Particularly, recent elegant advances have corroborated the high ability of this concept to establish new asymmetric catalytic reactions.[3] In addition to the fundamental significance, the related reactions have some practical advantages such as maximizing the operative efficiency, essential avoidance of an additional workup process, and reducing relevant pollution associated with stepwise catalytic protocols.

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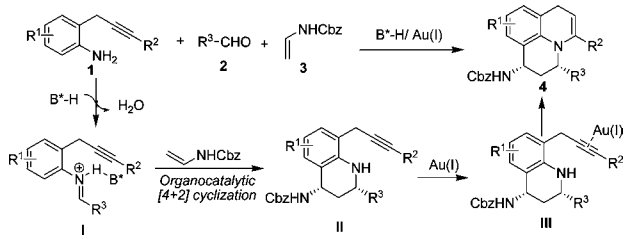
The direct generation of chiral molecules with structural complexity and diversity from simple substrates with high levels of stereochemical control constitutes an important, but still a formidable challenge in organic chemistry. Asymmetric multicomponent reactions provide an important tool to obtain this target.[4] The relay catalysis (or cascade catalysis) holds great potential, but has been recognized much less in the development of new multicomponent reactions for the stereoselective construction of structurally complex and diverse chiral heterocyclic architectures. Herein, we will report an asymmetric relay catalytic three-component reaction that consists of a sequential [4+2] cycloaddition and intramolecular hydroamination under the relay catalysis of a chiral Brønsted acid and achiral gold complex, highly yielding structurally complex julolidine derivatives, an important structural motif found in either biologically interesting substances[5] or organic materials,[6] with excellent levels of stereoselectivity.

Very recently, highly enantioselective Povarov reactions have been established by using binol-based phosphoric acid catalysts.[7] We and Che have demonstrated that the gold complexes and Brønsted acids can compatibly work in the relay catalysis for the consecutive hydroamination/transfer hydrogenation of alkynes, yielding chiral amines in excellent levels of enantioselectivity.[8] Inspired by these achievements, we proposed that a cascade reaction for the enantioselective direct generation of julolidine derivatives **4** might be able to commence with a Brønsted acid-catalyzed three-component inverse electron-demand aza-Diels−Alder reaction (Povarov reaction)[7a] of a 2-(2-propynyl)aniline derivative (**1**), aldehyde, and enamide, presumably producing an intermediate **II**, which should principally undergo a subsequent hydroamination reaction under the catalysis of an appropriate gold complex to give **4** via an active intermediate **III** (Scheme 1). Even though the related works have been

Scheme 1. General Concept for the Synthesis of Julolidines Derivatives by Cascade Reactions under the Relay Catalysis of Chiral Brønsted Acid and Gold Complex



available to provide some light for each individual step,[7,8] we believed that the validation of the proposed cascade reaction might still be the discovery of an efficient gold catalyst for the second annulation between secondary amine and carbon−carbon triple bond in view of the substrate-sensitive gold-catalyzed hydroaminations.[8,9]

The viability of the sequential reaction was first attempted by a reaction of **1a**, 4-bromobenzaldehyde **2a**, and an enamide **3** under the influence of a binary catalyst system comprised of 15 mol % of phosphoric acid **5** (Figure 1) and

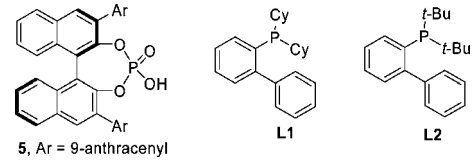
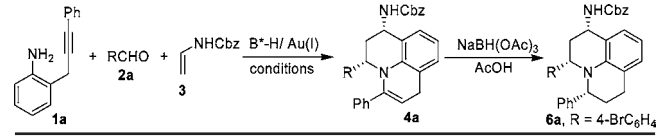


Figure 1. The Brønsted acid and phosphorus ligands used in this study.

10 mol % of $(Ph_3P)AuMe$.[8a] The reaction was conducted at −40 °C for 12 h and then at room temperature for 24 h. To our delight, the desired reaction occurred to give the predictable product **4a**, which was, however, too unstable to be isolated and thereby was immediately reduced with acetic acid and sodium triacetoxyborohydride,[10] leading to the generation of **6a** and its diastereomer in a total 30% yield with 98% ee for each diastereomer (Table 1, entry 1), but

Table 1. Screening Gold Complexes and Optimization of Reaction Conditions[a]



entry	Au(I) (mol %)	B*-H (mol %)	solvent	time (h)[b]	yield of **6a** (%)[c,e]	ee (%)[d,e]
1	$(Ph_3P)AuMe$(10)	15	$PhCH_3$	24	26(4)	98(98)
2	(L1)AuMe(10)	15	$PhCH_3$	24	53(9)	96(98)
3	(L2)AuMe(10)	15	$PhCH_3$	24	44(31)	97(98)
4	(L2)AuMe(10)	15	CH_2Cl_2	12	63(11)	97(96)
5	(L2)AuMe(10)	15	$CHCl_3$	12	38(9)	85(72)
6	(L2)AuMe(5)	15	CH_2Cl_2	12	51(5)	97(94)
7	(L2)AuMe(10)	10	CH_2Cl_2	12	57(9)	95(96)
8	$(Ph_3P)AuNTf_2$(10)	10	CH_2Cl_2	4	47(26)	94(95)

[a] The reaction of aniline **1a** (0.1 mmol), 4-bromobenzaldehyde (0.105 mmol), and **3** (0.3 mmol) was carried out at −40 °C for 12 h and room temperature for the indicated time, in the presence of 3 Å MS, phosphoric acid **5**, and an Au(I) complex as indicated. [b] The time refers to the hydroamination step at room temperature. [c] Isolated yield. [d] Determined by HPLC. [e] The data in parentheses are for the minor diastereomer of **6a**.

still with an accompanying trace amount of uncyclized Povarov product (**IIa**). Variation of the ligand from triphenylphosphine to 2-biphenylyldicyclohexylphosphine (L1)[9a] coordinating to gold(I) led to a significant improvement in the yield (62%) with excellent levels of enantioselectivity for both diastereomers, and significantly, no Povarov product

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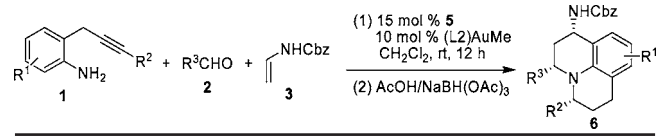
was detected (entry 2). A gold complex of 2-biphenylyldi-*tert*-butylphosphine (L2)[9a] provided an even higher total yield of **6a** and its diastereomer (75%, entry 3). The reaction conducted in dichloromethane not only maintained the yield and stereoselectivity in comparison of that in toluene, but also much favored the formation of **6a** (entry 4). Tuning of the reaction parameters including solvents and the stoichiometry of gold complex and phosphoric acid **5** led to no enhancement of the reaction performance (entries 5−7). The $Ph_3PAuNTf_2$[9b] showed high catalytic activity, but resulted in a slightly lower enantioselectivity than other gold catalyst partners of the Brønsted acid (entry 8). Screening different phosphoric acids[11] revealed that 3,3′-bis(9-anthracenyl)binol-derived phosphoric acid **5** is the most suitable catalyst for this sequential transformation, and notably, the 3,3′-bi(4-chlorophenyl)binol-derived phosphoric acid that afforded Povarov reaction in high stereoselectivity[7a] was unable to give satisfactory results (Table S1, see the Supporting Information).

We next investigated the generality of the protocol under the optimized conditions (Table 2). Electronically poor, neutral, or rich benzaldehydes were all able to participate in the smooth relay catalytic three-component reaction, which was treated with AcOH and $NaBH(OAc)_3$ to furnish julolidine derivatives in high yields and excellent levels of enantioselectivity (entries 1−11). Interestingly, substitution at either the para- or meta-position of the phenyl group was well tolerable and able to afford high stereoselectivity. Moreover, 2-furancarbaldehyde and an aliphatic aldehyde could be operative in fairly good yields and excellent enantioselectivity (entries 12 and 13). Variation of substitutents bonded to either C−C triple bond or to the benzene ring also underwent a clean reaction, giving the desired products in high yields and with excellent enantioselectivity (entries 14−16).

X-ray crystallographic analysis was used to determine the relative and absolute stereochemistry. The crystal structure[12] of **6i** shows that the Brønsted acid-catalyzed [4+2] cycloaddition in the cascade reaction and reduction of the enamine **4** generated from the subsequent hydroamination are both cis-selective and thereby (1*S*,3*S*,5*R*)-julolidine derivatives were preferentially produced.

Table 2. Generality of the Reaction[a]

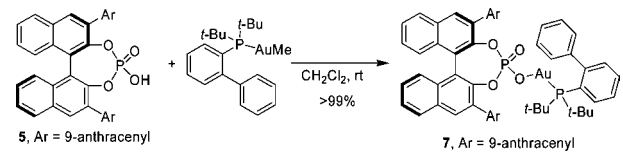


entry	$R^1/R^2/R^3$	6	yield (%)[b,d]	ee (%)[c,d]
1	H/Ph/Ph	**6b**	67(12)	92(92)
2	H/Ph/4-ClC_6H_4	**6c**	70(15)	96(97)
3	H/Ph/4-MeC_6H_4	**6d**	66(9)	92(92)
4	H/Ph/4-$MeOC_6H_4$	**6e**	61(7)	94(92)
5	H/Ph/4-CNC_6H_4	**6f**	70(14)	97(97)
6	H/Ph/4-$MeO_2CC_6H_4$	**6g**	72(11)	98(97)
7	H/Ph/4-$NO_2C_6H_4$	**6h**	56(12)	99(98)
8	H/Ph/3-ClC_6H_4	**6i**	63(6)	96(96)
9	H/Ph/3-$NO_2C_6H_4$	**6j**	68(14)	97(96)
10	H/Ph/3-$CF_3C_6H_4$	**6k**	62(11)	96(96)
11	H/Ph/3-$MeOC_6H_4$	***6l***	63(−)	93(−)
12	H/Ph/2-Furyl	**6m**	64(11)	92(90)
13	H/Ph/$PhCH_2CH_2$	**6n**	47(12)	96(96)
14	H/4-FC_6H_4/4-BrC_6H_4	**6o**	61(16)	97(96)
15	H/2-Naph/4-BrC_6H_4	**6p**	59(12)	97(97)
16	4-Cl/Ph/4-BrC_6H_4	**6q**	62(20)	>99(>99)

[a] The reaction of an aniline **1** (0.1 mmol), an aldehyde (0.105 mmol), and **3** (0.3 mmol) was carried out at −40 °C for 12 h and room temperature for 12 h, in the presence of 3 Å MS, 15% phosphoric acid **5**, and 10% (L2)AuMe. [b] Isolated yield. [c] Determined by HPLC. [d] The data in parentheses are for the minor diastereomer of **6**.

Previous works demonstrated that methyl−gold complex was able to react with some strong Brønsted acid to form a chiral cationic gold(I) complex.[13] To understand if the cationic gold(I) or methyl−gold complex participated in the catalysis, we performed ^{31}PNMR spectrometric studies on each gold catalyst species (Figure S1, SI). The ^{31}PNMR spectrum of a reaction mixture of (L2)AuMe shows a signal at 69.16 ppm. The phosphoric acid **5** gives a NMR peak at 0.55 ppm. The reaction mixture of (L2)AuMe and **5** with 1/1 ratio shows two new signals at 55.15 and 6.19 ppm, respectively, and the signals corresponding to (L2)AuMe and **5** both disappeared. The gold phosphate **7** in situ generated from a reaction mixture of silver phosphate complex with (L2)AuCl according to the literature procedure[14] showed two signals at 55.14 and 6.32 ppm, which are consistent with the signals assigned to the product from reaction of (L2)AuMe with **5**. Thus, the methyl−gold complex reacts readily with phosphoric acid to give the phosphates cleanly at room temperature (Scheme 2).

Scheme 2. The Reaction of (L2)AuMe and Phosphoric Acid **5**



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(12) CCDC 763776. See the Supporting Information for details. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 763776. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.

This relay catalytic reaction was believed to first undergo a Brønsted acid-catalyzed [4+2] cycloaddition reaction and a subsequent intramolecular hydramination reaction catalyzed by a gold complex. However, previous reports revealed that gold complexes serve as good Lewis acids capable of catalyzing asymmetric reactions.[15] To figure out if the gold complexes participated in accelerating the [4+2] reaction, we performed a control reaction of **1a** and 4-bromobenzaldehyde (**2a**) with enamide **3** in the presence of 10 mol % of the chiral gold phosphate **7** in situ generated from silver phosphate and (L2)AuCl (Figure S2, SI). However, the aza-Diels−Alder reaction was not observed by ^{1}HNMR, indicating that the gold complex used in this case is unable to catalyze the aza-Diels−Alder reaction (see the SI), instead the phosphoric acid served as the real catalyst of the first step. On the contrary, we have found that the cascade reaction occurred smoothly in the presence of 10 mol % of (L2)AuMe and **5** (Table 1, entry 7), indicating that the methyl−gold complex is difficult to completely convert into gold phosphate at −40 °C, otherwise the Povarov reaction would have not taken place as demonstrated by the control reaction. Instead, (L2)AuMe can be rapidly transformed into gold phosphate **7** with **5** at room temperature as shown by ^{31}PNMR spectra (Scheme 2 and Figure S1, SI), which served as the catalyst of intramolecular hydroamination.

Moreover, kinetic studies on the hydroamination reaction of **IIa** catalyzed by different gold complexes were performed to identify the real gold catalyst species for the second step of the cascade catalytic reaction (Figure 2). Methyl−gold complex showed a much lower catalytic activity than the corresponding gold phosphate by a factor of ca. 33. This observation, together with the fact that (L2)AuMe can be rapidly transformed into gold phosphate **7** with **5** at room temperature (Scheme 2), indicates that the gold phosphate **7** should be the real gold catalyst species for the hydroamination reaction. Previous reports on gold(I)-catalyzed hydroamination of alkynes showed that the presence of Brønsted acid facilitated the reaction to occur.[13] In this case, the presence of additional phosphoric acid **5** indeed provided a little faster reaction. Therefore, the phosphoric acid not only promotes the enantioselective [4+2] cycloaddition, but also assists the gold complex to catalyze the subsequent hydroamination reaction.

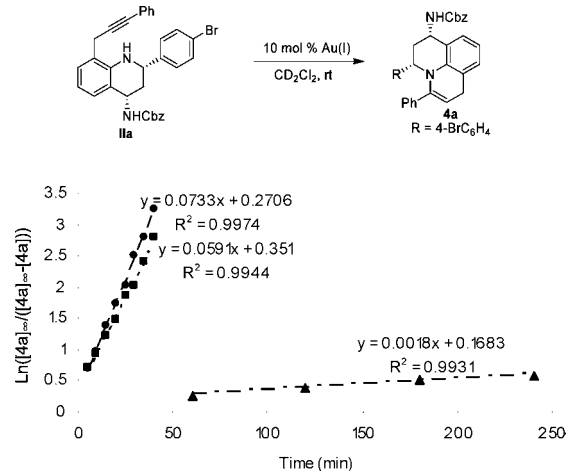

Figure 2. Kinetic studies on the hydroamination reaction of **IIa** by different gold complexes: (▲) the (L2)AuMe catalyzed reaction; (■) the reaction catalyzed by 10 mol % of **7**; (●) the reaction catalyzed by 10 mol % of **7** and **5**.

In summary, we have presented a highly enantioselective three-component cascade reaction, consisting of an enantioselective [4+2] cycloaddition reaction catalyzed by chiral phosphoric acid and a subsequent catalytic intramolecular hydroamination by a gold(I) complex, providing a unique method for the preparation of structurally diverse and complex julolidine derivatives in high optical purity. Kinetic studies reveal that the Brønsted acid is not only a chiral catalyst for the asymmetric [4+2] cycloaddition reaction, but also an assistant to facilitate the gold complex catalyzed hydroamination reaction. ^{31}P NMR and kinetic studies indicate that the methyl−gold complex easily reacts with phosphoric acid to give gold phosphate at room temperature, which shows higher catalytic activity.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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