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Highly Enantioselective Synthesis of Chiral Secondary Amines by Gold(I)/Chiral Brønsted Acid Catalyzed Tandem Intermolecular Hydroamination and Transfer Hydrogenation Reactions

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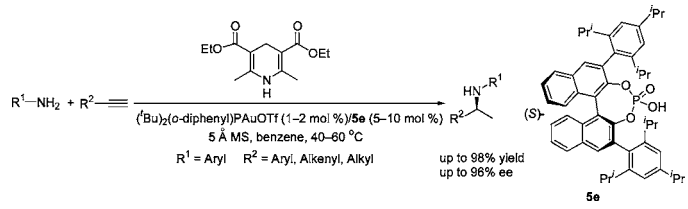
ABSTRACT



A method for the synthesis of enantiomerically enriched secondary amines with excellent ee values through the tandem intermolecular hydroamination/transfer hydrogenation of alkynes using a "gold(I) complex−chiral Brønsted acid" protocol is developed. The catalysis works for a wide variety of aryl, alkenyl, and aliphatic alkynes as well as anilines with different electronic properties.

Homogeneous gold catalysis has emerged to become a powerful tool for novel organic transformations.[1] However, compared with other transition metal catalysis, relatively few enantioselective transformations using gold(I) catalysts have been reported. This is possibly due to the linear coordination geometry of gold(I), which alleviates the steric interactions between the chiral inducer and the reactive functional group of the substrate.[2] To circumvent this problem, Toste and co-workers proposed the development of an efficient chiral counterion strategy and applied this strategy to accomplish the gold(I)-catalyzed highly enantioselective intramolecular hydroalkoxylation and hydroamination of allenes.[3] Despite this advance, the gold-catalyzed enantioselective organic transformations are in the rudimentary stage. In recent years, cooperative catalysis using protocols "a metal complex + an organic molecule" has been receiving a surge of interest in the context of developing novel organic transformations, owing to the cooperative effect in enhancing good reactivity and selectivity for the transformation reactions.[4] Inspired by Toste's paper,[3] we conceived that cooperative catalysis could

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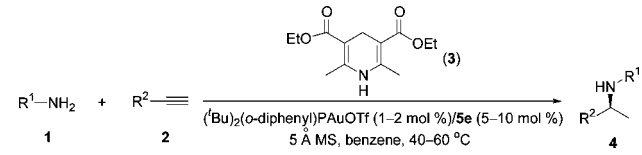
also be applied to gold catalysis for new enantioselective organic transformations, which would serve as a complementary approach to the conventional chiral gold(I)-catalyzed asymmetric organic synthesis.[2]

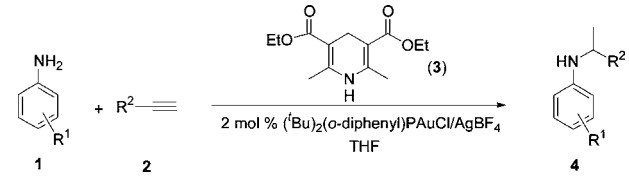
Chiral amines are ubiquitous structural motifs in a myriad of biologically active natural products and pharmaceutically active compounds.[5] A simple and powerful tool for preparing chiral amines is transition-metal-catalyzed hydroamination of unsaturated carbon−carbon bonds.[6] However, only a few of these methods could be applied to the intermolecular hydroamination for the synthesis of chiral amines with high product yield and high enantioselectivity.[7] Using alkynes as starting materials for the synthesis of chiral amines through intermolecular hydroamination has not been reported in literature.[1] Therefore, the development of new catalysis for intermolecular hydroamination of alkynes to form chiral amines would be invaluable to the synthetic organic chemistry community. As a continuation of our research in gold-catalyzed hydroamination reactions and related tandem reactions,[8] we report herein a highly enantioselective one-pot tandem intermolecular hydroamination/transfer hydrogenation of alkynes using a cooperative catalytic system composed of gold(I) complex and chiral Brønsted acid (Scheme 1). The transformation shows a very broad substrate scope toward diversely substituted chiral amines in up to 98% yields and up to 96% ee under mild conditions. After completion of this work and during the preparation of this manuscript, a paper by Gong and co-workers on consecutive intramolecular hydroamination/transfer hydrogenation using a gold complex/chiral Brønsted acid binary system for the enantioselective synthesis of tetrahydroquinolines was published.[9]

Scheme 1



We previously reported a gold(I)-catalyzed tandem hydroamination/hydroarylation reaction of aryl amines and alkynes for the synthesis of substituted 1,2-dihydroquinolines.[8b] Further studies revealed that a gold(I)-catalyzed reaction of *m*-anisidine (**1A**) with phenylacetylene (**2a**) in the presence of commercially available Hantzsch ester (**3**) afforded secondary amine **4Aa** (Table 1). Upon optimizing the reaction conditions by varying gold catalyst, solvent, temperature, and catalyst loading, we obtained **4Aa** in 94% yield from a reaction in THF at room temperature for 31 h using 2 mol % of $(^t\mathrm{Bu})_2$(*o*-biphenyl)PAuCl/$AgBF_4$ (Table 1, entry 1). Under similar conditions, the reaction for a variety of substituted anilines and alkynes gave secondary amines in 76−95% yields (Table 1, entries 2−10).

Table 1. Gold(I)-Catalyzed Tandem Reactions between Aryl Amines and Alkynes[a]



entry	R^1	R^2	product	*t* (h)	yield (%)[b]
1	3-MeO (**1A**)	Ph (**2a**)	**4Aa**	31	94
2	4-MeO (**1B**)	Ph (**2a**)	**4Ba**	32	95
3	3,5-$(MeO)_2$ (**1F**)	Ph (**2a**)	**4Fa**	24	86
4	H (**1H**)	Ph (**2a**)	**4Ha**	48	90
5	4-Cl (**1I**)	Ph (**2a**)	**4Ia**	72	78
6	3-MeO (**1A**)	*p*-MeC_6H_4 (**2b**)	**4Ab**	72	86
7	3-MeO (**1A**)	*o*-MeC_6H_4 (**2c**)	**4Ac**	72	90
8	3-MeO (**1A**)	*m*-$MeOC_6H_4$ (**2e**)	**4Ae**	72	76
9	3-MeO (**1A**)	*p*-FC_6H_4 (**2g**)	**4Ag**	48	86
10	3-MeO (**1A**)	*n*-butyl (**2j**)	**4Aj**	48	92

[a] Reaction Conditions: amine (0.5 mmol), alkyne (1.0 mmol), **3** (0.75 mmol), $(^t\mathrm{Bu})_2$(*o*-biphenyl)PAuCl/$AgBF_4$ (0.01 mmol), and THF (2 mL), rt to 60 °C. [b] Isolated yield based on aryl amine.

To render the reaction enantioselective, we examined various chiral diphosphine gold(I) catalysts; however, poor ee and low yields of **4Aa** were observed (Table S1 in Supporting Information). In view of the efficiency of chiral phosphoric acids[10] in catalyzing the enantioselective transfer

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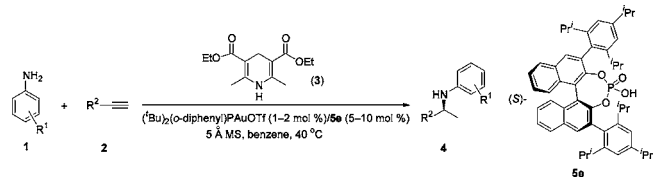
Table 2. Gold(I)/Chiral Phosphoric Acid Catalyzed Tandem Reactions between Aryl Amines and Alkynes[a]



entry	R^1	R^2	product	t (h)	yield (%)[b]	ee (%)[c]
1	3-MeO (**1A**)	Ph (**2a**)	**4Aa**	72	85	94
2	4-MeO (**1B**)	Ph (**2a**)	**4Ba**	72	86	89
3	4-PhO(**1C**)	Ph (**2a**)	**4Ca**	72	87	85
4[d]	4-Me (**1D**)	Ph (**2a**)	**4Da**	120	95	90
5	4-Ph (**1E**)	Ph (**2a**)	**4Ea**	72	70	90
6	3,5-$(MeO)_2$ (**1F**)	Ph (**2a**)	**4Fa**	72	75	96
7	3,5-$(Me)_2$ (**1G**)	Ph (**2a**)	**4Ga**	72	78	95
8[d]	H (**1H**)	Ph (**2a**)	**4Ha**	120	79	92
9[d]	4-Cl (**1I**)	Ph (**2a**)	**4Ia**	144	91	88
10[d]	4-Br (**1J**)	Ph (**2a**)	**4Ja**	144	96	88
11	3-MeO (**1A**)	p-MeC_6H_4 (**2b**)	**4Ab**	96	91	94
12	3-MeO (**1A**)	o-MeC_6H_4 (**2c**)	**4Ac**	96	87	91
13	3-MeO (**1A**)	p-$MeOC_6H_4$ (**2d**)	**4Ad**	96	98	89
14	3-MeO (**1A**)	m-$MeOC_6H_4$ (**2e**)	**4Ae**	96	93	90
15	3-MeO (**1A**)	p-PhC_6H_4 (**2f**)	**4Af**	96	92	92
16	3-MeO (**1A**)	p-FC_6H_4 (**2g**)	**4Ag**	96	94	83
17[d]	3-MeO (**1A**)	p-$CF_3C_6H_4$ (**2h**)	**4Ah**	120	90	90
18[d]	3-MeO (**1A**)	p-CNC_6H_4 (**2i**)	**4Ai**	120	81	86
19	3-MeO (**1A**)	n-butyl (**2j**)	**4Aj**	72	85	83
20	3-MeO (**1A**)	n-hexyl (**2k**)	**4Ak**	96	86	93
21	3-MeO (**1A**)	n-octyl (**2l**)	**4Al**	72	91	95
22	3-MeO (**1A**)	i-pentyl (**2m**)	**4Am**	96	79	86
23	3-MeO (**1A**)	$Ph(CH_2)_2$ (**2n**)	**4An**	72	91	92
24	3-MeO (**1A**)	cyclohexyl (**2o**)	**4Ao**	120	75	95
25[d]	3-MeO (**1A**)	cyclohexenyl (**2p**)	**4Ao**	120	54	95
26	3-MeO (**1A**)	cyclopropyl (**2q**)	**4Aq**	40	98	83
27	3-MeO (**1A**)	$Me_2C{=}CH(CH_2)_2$ (**2r**)	**4Ar**	72	88	91

[a] Reaction conditions: amine (0.2 mmol), alkyne (0.4 mmol), **3** (0.3 mmol), (^{t}Bu)$_2$(o-biphenyl)PAuOTf (1 mol %), **5e** (5 mol %), benzene (3 mL), and 5 Å MS (1 g), 40 °C. **5e** = (*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate. [b] Isolated yield based on aromatic amine. [c] Determined by chiral HPLC; configuration assigned by comparison with the literature (see Supporting Information for details). [d] Reaction conditions: amine (0.2 mmol), phenylacetylene (0.4 mmol), **3** (0.4 mmol) added in two portions (60 h + 60 h), (^{t}Bu)$_2$(o-biphenyl)PAuOTf (2 mol %), **5e** (10 mol %), benzene (3 mL), and 5 Å MS (1 g), 60 °C.

hydrogenation of imines[11] and the possible formation of a ketimine intermediate via gold(I)-catalyzed intermolecular hydroamination,[8b] we envisioned that a binary catalytic system composed of a gold(I) complex and a chiral Brønsted acid could be used to prepare chiral amines. A challenge to achieve excellent enantioselectivity in this cooperative catalysis is to suppress the transfer hydrogenation of ketimines catalyzed by the gold(I) complex. Using **5a** (10 mol %) as a chiral Brønsted acid, reaction of **1A** with **2a** and **3** catalyzed by (^{t}Bu)$_2$(o-biphenyl)PAuBF$_4$ (3 mol %) gave **4Aa** in 84% yield and 32% ee (Table S2 in Supporting Information). After optimization of reaction conditions, **4Aa** was obtained in 85% yield and 94% ee from a reaction in benzene in the presence of activated, powdered molecular sieves (MS, 5 Å) using (^{t}Bu)$_2$(o-biphenyl)PAuOTf and 2,4,6-triisopropylphenyl-derived chiral phosphoric acid **5e** as catalysts (see Table S2 in Supporting Information). Almost the same product yield and ee value could still be obtained upon lowering the gold(I) catalyst loading from 3 to 1 mol % or the loading of **5e** from 10 to 5 mol %. The reaction was not catalyzed by **5e** alone.

Under the optimal conditions, reaction of **2a** with a series of *para*-, *meta*-, or disubstituted anilines (**1B**−**G**) bearing electron-donating substituents afforded chiral amines **4Ba**−**Ga** in 70−95% yields and 85−96% ee (Table 2, entries 2−7). For *para*-substituted anilines **1I**,**J** bearing electron-withdrawing groups, their reactions gave **4Ia**,**Ja** in 91% and 96% yields and both in 88% ee, although a longer reaction time, a higher temperature (60 °C), and an increased catalyst loading were required for complete substrate conversion (entries 9 and 10).

A wide variety of alkynes (**2b**−**r**) were similarly treated with *m*-anisidine (**1A**) to furnish diversely substituted chiral

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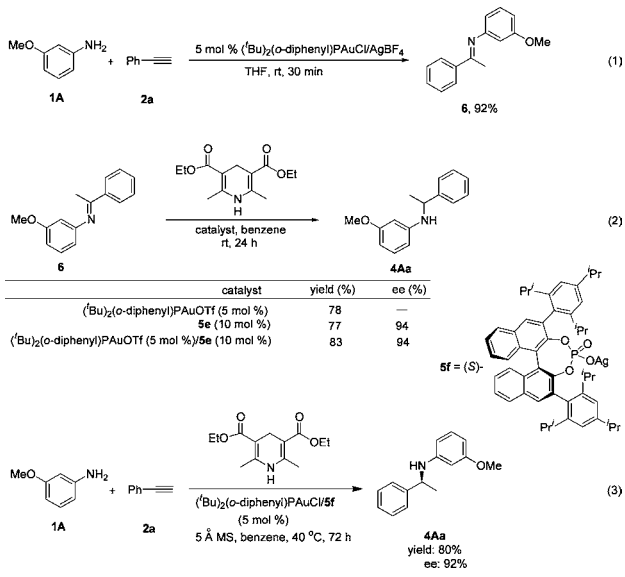
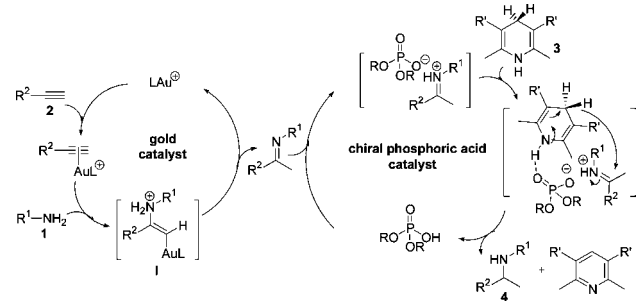
amines **4Ab**−**Ar** (Table 2). Generally, the reaction works well for aryl alkynes possessing electron-donating/-withdrawing *ortho*, *meta*, or *para* substituents (entries 11−18). The present cooperative catalysis could be applied to aliphatic alkynes **2j**−**r**, although *N*-aryl ketimines with dialkyl substituents have rarely been reported to give the corresponding chiral amines with both excellent product yield and high enantioselectivity in related organocatalysis.[11] Both linear and branched aliphatic alkynes gave the corresponding chiral amines **4Aj**−**Am** in good to excellent yields (79−91%) and enantioselectivities (83−95%) (entries 19−22). Cyclic aliphatic alkynes are also applicable without loss in reaction efficiency and enantiocontrol (entries 23−26). 1-Ethynylcyclohex-1-ene (**2p**) underwent this tandem reaction to give **4Ao** with 95% ee via a conjugate reduction step, albeit with a moderate yield (54%) (entry 25). Notably, the catalytic system tolerates other reactive groups, such as CN, cyclopropyl, and alkenyl in the alkyne substrates (entries 18, 26, and 27).

A series of control experiments were conducted to gain insight into the mechanism of the transformation. In the absence of ethyl Hanzsch ester (**3**), ketimine **6** was afforded in 92% yield with (^{t}Bu)$_2$(*o*-biphenyl)PAuCl/ $AgBF_4$ (eq 1); however, no reaction was found when **5e** alone was used as the catalyst. This result reveals that the gold(I)-catalyzed hydroamination is the first step in this tandem sequence. Electrospray ionization mass spectroscopic analysis of a solution of aniline, phenylacetylene, and (^{t}Bu)$_2$(*o*-biphenyl)PAuOTf (20 mol %) in CH_2Cl_2 after stirring for 15 min at room temperature showed a peak at *m*/*z* 690, which is consistent with the intermediacy of **I** depicted in Scheme 2. Subsequent treatment of the ketimine **6** with **3** at room temperature for 24 h in the presence of gold(I) complex alone or chiral phosphoric acid **5e** alone gave **4Aa** in similar yields. Despite the fact that gold(I) complex can efficiently catalyze the transfer hydrogenation of ketimines, in this work, excellent enantioselectivity (94%) has been obtained in the presence of both gold(I) complex and **5e**, revealing that the



Scheme 2



chiral phosphoric acid plays a dominant role in the reduction process for obtaining excellent enantioselectivity (eq 2). However, we could not exclude the possibility of an exchange of the metal counteranion, which could lead to the formation of a gold(I) complex cation-chiral counteranion ion pair[3] to catalyze the subsequent reaction, because the reaction of **1A** with **2a** catalyzed by gold phosphate, derived from (^{t}Bu)$_2$(*o*-biphenyl)PAuCl and **5f**, gave **4Aa** in 80% yield and 92% ee (eq 3). On the basis of these observations, a reaction mechanism for the formation of chiral amines from the cooperative gold(I)/chiral phosphoric acid catalyzed reactions of **1** with **2** in the presence of **3** is proposed and depicted in Scheme 2. The reaction mechanism involves gold(I)-catalyzed intermolecular hydroamination of alkyne to generate the ketimine intermediate,[8,12] and the subsequent chiral phosphoric acid catalyzed transfer hydrogenation of this intermediate similar to that reported by Goodman and co-workers.[13]

In summary, we have demonstrated a highly enantioselective tandem intermolecular hydroamination/transfer hydrogenation of alkynes using a protocol composed of gold(I) complex−chiral Brønsted acid. A wide variety of aryl, alkenyl, and aliphatic alkynes as well as anilines with different electronic properties can be tolerated. This approach combines the advantages of both gold(I) and organocatalysis, leading to an efficient synthesis of highly enantiomerically enriched chiral secondary amine compounds.

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Supporting Information Available: Experimental procedures, product characterizations, Tables S1 and S2, and Figure S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For an excellent theoretical study on a related mechanism, see: Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741.