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Highly Efficient and Diastereoselective Gold(I)-Catalyzed Synthesis of Tertiary Amines from Secondary Amines and Alkynes: Substrate Scope and Mechanistic Insights

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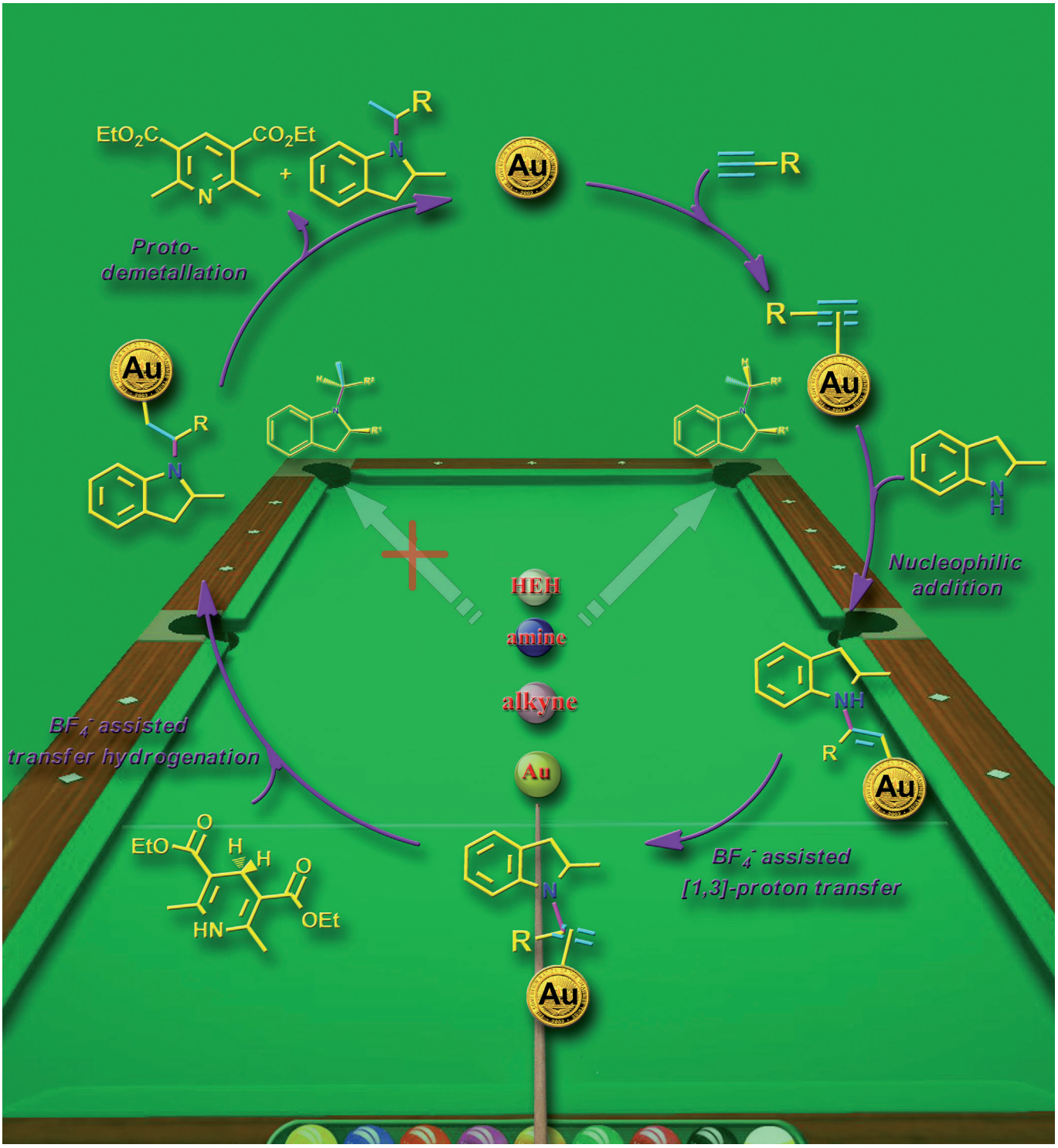


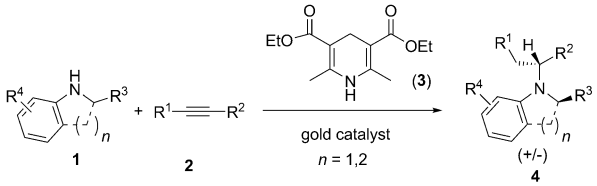
Abstract: An efficient method for the synthesis of tertiary amines through a gold(I)-catalyzed tandem reaction of alkynes with secondary amines has been developed. In the presence of ethyl Hantzsch ester and [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$ (2 mol%), a variety of secondary amines bearing electron-deficient and electron-rich substituents and a wide range of alkynes, including terminal and internal aryl alkynes, aliphatic alkynes, and electron-deficient alkynes, underwent a tandem reaction to afford the corresponding tertiary amines in up to 99% yield. For indolines bearing a preexisting chiral center, their reactions with alkynes in the presence of ethyl Hantzsch ester catalyzed by [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$ (2 mol%) afforded tertiary amines in excellent yields and with good to excellent diastereoselectivity. All of these organic transformations can be conducted as a one-pot reaction from simple and readily available starting materials without the need of isolation of air/moisture-sensitive enamine intermediates, and under mild reaction conditions (mostly room temperature and mild reducing agents). Mechanistic studies by NMR spectroscopy, ESI-MS, isotope labeling studies, and DFT calculations on this gold(I)-catalyzed tandem reaction reveal that the first step involving a monomeric cationic gold(I)–alkyne intermediate is more likely than a gold(I)–amine intermediate, a three-coordinate gold(I) intermediate, or a dinuclear gold(I)–alkyne intermediate. These studies also support the proposed reaction pathway, which involves a gold(I)-coordinated enamine complex as a key intermediate for the subsequent transfer hydrogenation with a hydride source, and reveal the intrinsic stereospecific nature of these transformations observed in the experiments.

Keywords: alkynes · density functional calculations · diastereoselectivity · gold · tertiary amines

Introduction

Transition-metal-catalyzed tandem carbon–carbon and carbon–heteroatom bond-formation reactions have emerged as powerful tools for the synthesis of valuable synthetic building blocks starting from relatively simple and readily available precursors.[1] Among these transition-metal catalysts, the use of gold complexes as catalysts has recently been proven to be a useful approach for the synthesis of diverse classes of organic compounds with complexity, selectivity, and high atom economy under mild reaction conditions.[2] In this area, we have developed a series of gold-catalyzed tandem reactions for the construction of synthetically useful polycyclic compounds.[3]

We recently reported a gold(I)-catalyzed tandem reaction of primary amines with alkynes to give secondary amines. The mechanism of the reaction involves initial formation of an imine intermediate through an intermolecular hydroamination process followed by a subsequent transfer hydrogenation with Hantzsch ester (HEH).[3d] Subsequently, we explored whether secondary amines could also undergo this similar reaction through tandem intermolecular hydroamination and transfer hydrogenation to give tertiary amines. Some studies, including our own work, have revealed that cationic gold(I) complexes bearing bulky phosphine or NHC ligands could catalyze the intermolecular hydroamination of alkynes with secondary amines to give the corresponding enamines.[3b,4,5] Compared to imines or iminium ions that display high reactivity toward Hantzsch ester,[6] unfunctionalized enamines show diminished electrophilic character. Their low propensity to react with hydrides under mild reaction conditions is attributed to the delocalization of the lone-pair electrons of nitrogen atom to the C–C double bond.[7,8] In the literature, gold catalysts have been found to display an exceptional ability to activate C–C multiple bonds for nucleophilic attack through π-acid activation.[9] We envisioned that gold complex could coordinate to the C–C double bond of the enamine intermediate generated in situ. The coordination would cause enamine intermediate less electron rich and thereby increase the reactivity of the double bond of enamine for nucleophilic attack.[9c] The gold-stabilized enamine intermediate could then enter the subsequent catalytic transfer hydrogenation with a hydride source such as HEH. This new method for the synthesis of tertiary amines from secondary amines and alkynes catalyzed by gold(I) complex is reported herein (Scheme 1).



Scheme 1. The highly selective formation of tertiary amines from the gold(I)-catalyzed tandem reaction.

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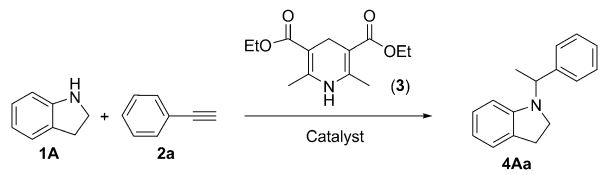
Tertiary amines constitute a valuable class of chemical compounds that have potential for pharmaceutical, agrochemical, and industrial applications.[10] For this reason, there has been continued interest in the development of efficient methods for the synthesis of tertiary amines bearing multiple and diverse substituent pattern. The reduction of unfunctionalized tertiary enamines employing nucleophilic hydride donors is a useful transformation for the synthesis of tertiary amines;[11] however, there are a number of significant challenges impeding such developments. These include the use of enamine substrates that are not always easy to be prepared due to stability issue.[7] On the other hand, these reduction methods normally require the use of highly reactive reagents, such as aluminum hydride and boron hydride as the hydride sources,[5b,11] thus rendering the synthetic utility of such hydride reagents limited to the harsh reaction conditions, low functional-group tolerance and tedious purification procedures.

Over the past decades, air- and moisture-stable Hantzsch ester has been introduced as a convenient reagent for a number of transfer hydrogenation reactions of unsaturated organic compounds.[6,12] However, only a few examples on the reduction of unfunctionalized tertiary enamines by using HEH as the reducing agent have been reported, and all of these reduction reactions require the use of stoichiometric or excess amounts of strong Brønsted acids to facilitate the formation of iminium ion intermediate.[13] Therefore, the development of an efficient catalyst to stabilize unfunctionalized tertiary enamines for subsequent reduction by mild reducing agent would be highly desirable. The method reported herein (Scheme 1) is useful for the construction of tertiary amines bearing multiple substituents using a mild reducing agent, such as HEH, and without the need of workup and isolation of air/moisture-sensitive tertiary enamine intermediate(s). Also, this process proceeds under mild conditions and leads to tertiary amines, with a very broad substrate scope, in up to 99% yields. When secondary amines bearing a preexisting chiral center were employed, excellent diastereoselectivity (up to >20:1) was achieved. Also reported here are our mechanistic studies of the gold(I)-catalyzed tandem reaction of alkynes with secondary amines employing a combination of experimental and computational techniques.

Results and Discussion

Gold(I)-catalyzed tandem synthesis of tertiary amines: Our prior observation that gold(I) complexes can efficiently catalyze the synthesis of secondary amines from primary amines and alkynes in the presence of HEH,[3d] and the possibility that this catalyst could lead to the synthesis of tertiary amine when secondary amine is used as a substrate, led us to further explore the substrate scope and mechanism of this reaction. To do so, we initiated these investigations by examining the reaction of indoline (**1A**) with phenylacetylene (**2a**) in the presence of commercially available Hantzsch ester (**3**) catalyzed by a combination of [(Ph$_3$P)AuCl] (5 mol%) and AgBF$_4$. We found that [(Ph$_3$P)AuCl]/AgBF$_4$ could catalyze this reaction in CH$_3$NO$_2$ at 60°C to form the desired product **4Aa** in 42% yield (Table 1, entry 1). Further investigation showed that the solvent had no significant effect on the conversion of this tandem reaction (Table 1, entries 1–5). We then turned our attention to examine the activity of other gold catalysts on this reaction. Simple gold salts, such as AuCl or KAuCl$_4$, all failed to give the desired product in good yield (Table 1, entries 6 and 7). While using a combination of (NHC)AuCl/AgBF$_4$ (5 mol%; NHC = *N*,*N*′-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) as the catalyst, which was previously reported by Nolan and co-workers to have useful applications in gold catalysis,[14] the desired product was formed in 78% yield in THF at room temperature (Table 1, entry 8). The use of [{(*t*Bu)$_2$(*o*-biphenyl)P}AuCl]/AgBF$_4$, a catalyst previously reported by Echavarren and co-workers,[15] afforded **4Aa** in 98% yield for only 8 h at room temperature (Table 1, entry 9). We next studied this reaction at room temperature in the presence of [{(*t*Bu)$_2$(*o*-biphenyl)P}AuCl]/AgBF$_4$ with different loadings. It should be noted that the catalyst loading could be reduced from 5 to 2 mol% without affecting the yield of **4Aa** (Table 1, entry 10). Notably, a control experiment revealed that AgBF$_4$ as the catalyst gave **4Aa** in only 6% NMR yield (Table 1, entry 13). The optimal reaction conditions were found to be of [{(*t*Bu)$_2$(*o*-biphenyl)P}AuCl]/AgBF$_4$ (2 mol%) with THF as the solvent at

Table 1. Optimization of reaction conditions for the synthesis of tertiary amine.[a]



	Catalyst	Solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	[(Ph$_3$P)AuCl]/AgBF$_4$	CH$_3$NO$_2$	60	16	42
2	[(Ph$_3$P)AuCl]/AgBF$_4$	CH$_3$CN	60	16	20
3	[(Ph$_3$P)AuCl]/AgBF$_4$	EtOH	60	16	26
4	[(Ph$_3$P)AuCl]/AgBF$_4$	toluene	60	16	24
5	[(Ph$_3$P)AuCl]/AgBF$_4$	THF	60	16	52
6	AuCl	THF	60	21	21
7	KAuCl$_4$	THF	60	21	11
8	(NHC)AuCl[c]/AgBF$_4$	THF	RT	21	78
9	[{(*t*Bu)$_2$(*o*-biphenyl)P}AuCl]/AgBF$_4$	THF	RT	8	98
10[d]	[{(*t*Bu)$_2$(*o*-biphenyl)P}AuCl]/AgBF$_4$	THF	RT	10	96
11[e]	[{(*t*Bu)$_2$(*o*-biphenyl)P}AuCl]/AgBF$_4$	THF	RT	18	63
12[f]	[{(*t*Bu)$_2$(*o*-biphenyl)P}AuCl]/AgBF$_4$	THF	RT	18	34
13	AgBF$_4$	THF	60	21	6

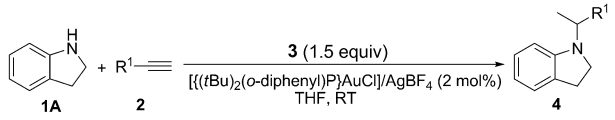
[a] Reaction conditions: indoline (0.5 mmol), phenylacetylene (0.6 mmol), ethyl Hantzsch ester (**3**) (0.75 mmol), and catalyst (5 mol%). [b] Yield was determined by ^{1}H NMR spectroscopy. [c] NHC = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [d] Catalyst loading was 2 mol%. [e] Catalyst loading was 1 mol%. [f] Catalyst loading was 0.5 mol%.

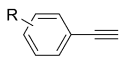
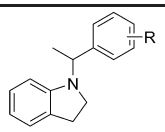
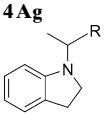
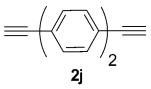
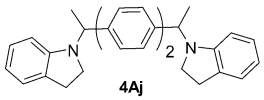
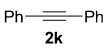
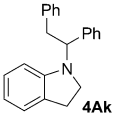
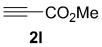
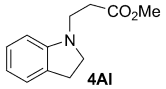
room temperature for 10 h, and gave the product **4Aa** in 96% yield (Table 1, entry 10).

Under the optimized reaction conditions, we examined the substrate scope of the gold(I)-catalyzed tandem reaction. A variety of aromatic alkynes were similarly treated with indoline (**1A**) in the presence of of [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$ (2 mol%). As depicted in Table 2, under the optimized conditions, the functional groups, methyl, methoxy, fluoro, and CN groups at the *para*-position of the benzene ring were well-tolerated, giving the corresponding products in excellent yields (Table 2, entries 2, 3, 6, and 7). Notably, the introduction of a methoxy group at the *para*-, *meta*-, or *ortho*-position in the phenyl group of aromatic alkynes did not affect the product yield either (Table 2, entries 3–5). Aliphatic alkynes were also efficiently used as the substrates in the presence of gold catalyst to afford the corresponding tertiary amines **4Ah** and **4Ai** in excellent yields (Table 2, entries 8 and 9). Interestingly, a good yield (79%) of **4Aj** was achieved when 4,4′-diethynylbiphenyl (**2j**) bearing two terminal alkyne groups was treated with **1A** (2.5 equiv) under similar reaction conditions (Table 2, entry 10). We then turned our attention to the reaction with internal alkynes. For example, the catalytic reaction of 1,2-biphenylethyne (**2k**) with **1A** in the presence of [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$ at 40°C led to the corresponding product **4Ak**, albeit with decreased product yield (44%; Table 2, entry 11). It is also worth noting that the reaction with electron-deficient alkynes such as methyl propiolate (**2l**) proceeded smoothly, but only a moderate yield (54%) was achieved under the same conditions (Table 2, entry 12). These results indicate that a variety of alkynes, from electron-rich ones including terminal and internal aryl alkynes, aliphatic alkynes, to electron-deficient alkyne, can be used as substrates for this gold(I)-catalyzed tandem reaction.

The gold(I)-catalyzed tandem reaction of various secondary amines with phenylacetylene (**2a**) was performed under the optimized conditions as depicted in Table 3. The reaction of **2a** with 5-bromoindoline (**1B**) in the presence of [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$ (2 mol%) at room temperature gave the corresponding product **4Ba** in 99% yield (Table 3, entry 1). Furthermore, 1,2,3,4-tetrahydroquinolines were also applicable, and the reaction afforded tertiary

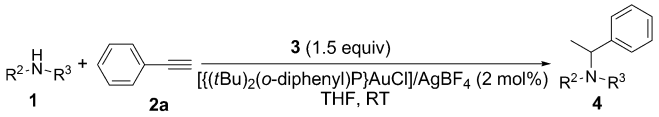
Table 2. [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$-catalyzed synthesis of tertiary amines with various alkynes.[a]

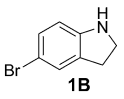
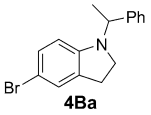
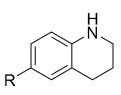
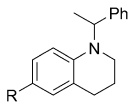
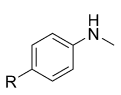
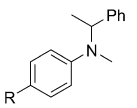


	Alkyne	Product	t [h]	Yield [%][b]
				
1	R = H (**2a**)	**4Aa**	10	96
2	R = 4-Me (**2b**)	**4Ab**	10	94
3	R = 4-OMe (**2c**)	**4Ac**	8	98
4	R = 3-OMe (**d**)	**4Ad**	8	92
5	R = 2-OMe (**2e**)	**4Ae**	8	95
6	R = 4-F (**2f**)	**4Af**	16	97
7	R = 4-CN (**2g**)	**4Ag**	24	91
				
8	R = *n*Bu (**2h**)	**4Ah**	17	92
9	R = *n*-hexyl (**2i**)	**4Ai**	16	90
10[c]	 **2j**	 **4Aj**	24	79
11[d]	 **2k**	 **4Ak**	24	44
12	 **2l**	 **4Al**	24	54

[a] Reaction conditions: indoline (0.5 mmol), alkyne (0.6 mmol), ethyl Hantzsch ester (**3**) (0.75 mmol), [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$ (2 mol%), THF (2 mL) at room temperature. [b] Isolated yield based on indoline. [c] Alkyne:indoline = 1:2.5; isolated yield based on alkyne. [d] Reaction temperature was 40°C.

Table 3. [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$-catalyzed synthesis of tertiary amines with various secondary amines.[a]



	Amine	Product	t [h]	Yield [%][b]
1	 **1B**	 **4Ba**	12	99
				
2[c]	R = H (**1C**)	**4Ca**	21	85
3[c]	R = OMe (**1D**)	**4Da**	26	94
				
4[c]	R = H (**1E**)	**4Ea**	26	86
5[c]	R = OMe (**1F**)	**4Fa**	26	98

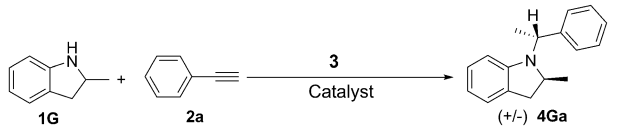
[a] Reaction conditions: secondary amine (0.5 mmol), phenylacetylene (0.6 mmol), ethyl Hantzsch ester (**3**) (0.75 mmol), [{(tBu)$_2$(o-biphenyl)-P}AuCl]/AgBF$_4$ (2 mol%), THF (2 mL) at room temperature. [b] Isolated yield based on amine. [c] Reaction temperature was 60°C.

amines **4Ca** and **4Da** in 85 and 94% yields, respectively (Table 3, entries 2 and 3).[16] Simple acyclic amines were also effective substrates. The reactions of 4-methoxy-*N*-methylaniline (**1E**) or *N*-methylaniline (**1F**) with **2a** in the presence of [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$ (2 mol%) at 60°C led to the corresponding amines **4Ea** or **4Fa** in 86 and 98% yields, respectively (Table 3, entries 4 and 5).

Gold(I)-catalyzed, diastereoselective synthesis of tertiary amines: An objective of developing a new metal-catalyzed reaction stems from the expectation that this new reaction would occur, not only with a high catalytic activity, but also with a high degree of selectivity.[17] In this work, we investigated the gold(I)-catalyzed reaction of alkynes with secondary amines containing a preexisting chiral center. It was anticipated that this preexisting chiral center in secondary amine would induce a high degree of stereospecificity in the formation of tertiary amines having two stereocenters.

To ascertain the feasibility of this hypothesis, we carried out a catalytic diastereoselective tandem reaction of 2-methylindoline (**1G**) with phenylacetylene (**2a**) in the presence of ethyl Hantzsch ester (**3**) and [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$ (2 mol%). To our delight, the desired product **4Ga** was obtained with a diastereomeric ratio of 10:1 in 92% yield (Table 4, entry 1). To improve the diastereoselectivity, a panel of gold(I) complexes with different ancillary ligands were screened for the activity and diastereo-induction in the tandem reaction. No reaction was observed when [(Ph$_3$P)AuCl]/AgBF$_4$ was used as the catalyst (Table 4, entry 2). Use of gold complexes bearing different auxiliary ligands including NHC, (Cy)$_2$(2′,4′,6′-triisopropyl-o-biphenyl)P and (tBu)$_2$(2′,4′,6′-triisopropyl-o-biphenyl)P also resulted in the formation of product **4Ga** in moderate to good yields, but similar diastereoselectivity was achieved in all cases (Table 4, entries 3–5). Further screening of solvents revealed that benzene gave the best result for the formation of the desired product with improved diastereoselectivity (15:1) (Table 4, entry 8), while the polar solvents THF and acetonitrile both gave lower levels of diastereoselectivity (Table 4, entries 1 and 6). Another hydride source, *tert*-butyl Hantzsch ester, was also tested under the same reaction conditions; however, lower yield and diastereoselectivity were found comparing with ethyl Hantszch ester (Table 4, entry 9).

Table 4. Optimization of reaction conditions for the diastereoselective synthesis of tertiary amines.[a]



	Catalyst	Solvent	t [h]	Yield [%][b]	d.r.[c]
1	[{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$	THF	17	92	10:1
2	[(Ph$_3$P)AuCl]/AgBF$_4$	THF	47	–[d]	–[d]
3	(NHC)AuCl[e]/AgBF$_4$	THF	47	89	9:1
4	[(L^1)AuCl][f]/AgBF$_4$	THF	47	61	9:1
5	[(L^2)AuCl][g]/AgBF$_4$	THF	47	58	8:1
6	[{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$	CH$_3$CN	39	69	6:1
7	[{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$	toluene	17	90	14:1
8	[{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$	benzene	17	95	15:1
9[h]	[{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$	benzene	36	86	8:1

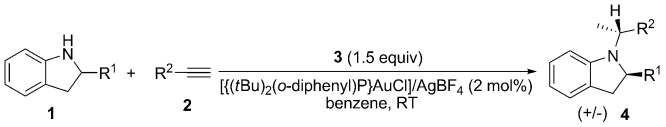
[a] Reaction conditions: 2-methylindoline (0.5 mmol), phenylacetylene (0.6 mmol), ethyl Hantzsch ester (**3**) (0.75 mmol), catalyst (2 mol%), solvent (2 mL) at room temperature. [b] Isolated yield based on amine. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy; major isomer shown. [d] Product was not detected. [e] NHC = *N*,*N*′-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene. [f] L^1 = {(Cy)$_2$(2′,4′,6′-triisopropyl-o-biphenyl)P}. [g] L^2 = {(tBu)$_2$(2′,4′,6′-triisopropyl-o-biphenyl)P}. [h] *tert*-butyl Hantzsch ester was used as the hydride source.

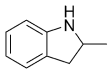
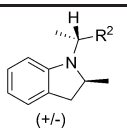
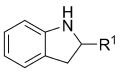
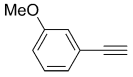
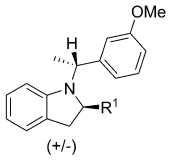
As highly diastereoselective formation of tertiary amine catalyzed by [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgBF$_4$ (2 mol%) with benzene as solvent had been achieved for the model substrate, the scope of this tandem reaction with regard to alkynes and indolines bearing a preexisting chiral center was next examined. The results are summarized in Table 5. The generality of the protocol is proven by the reactions of a series of alkynes with amines, giving the desired products in excellent yields with good levels of diastereoselectivity. Aryl alkynes with an electron-donating *para*-substituent on the phenyl ring could be successfully employed to afford tertiary amines in 90–99% yields with good diastereoselectivity (up to 15:1; Table 5, entries 1, 2, and 5). Notably, for *meta*- and *ortho*-substituted aryl alkynes bearing electron-donating group, such as *o*-, *m*-methoxy- and *o*-methyl aryl alkynes, the corresponding products **4Gd**, **4Ge**, and **4Gm** were obtained with improved diastereoselectivity (up to 19:1) in 83–97% yields (Table 5, entries 3, 4, and 6). The electron-deficient aryl alkyne **2n** gave the product **4Gn** as a 12:1 mixture of diastereomers in excellent yield (93%), although an increased catalyst loading, a higher reaction temperature (40°C) and a longer reaction time in the presence of activated, powdered molecular sieves (MS, 5 Å) were required for complete substrate conversion (Table 5, entry 7).

Next, we turned our attention to this tandem reaction of 1-ethynyl-3-methoxybenzene (**2d**) with other indolines that have an α-substituent under the same reaction conditions. With 2-phenethylindoline (**1H**) as the secondary amine component, **4Hd** was obtained in 92% yield with a diastereometric ratio of 14:1 (Table 5, entry 8). The introduction of a phenyl group possessing either electron-donating or electron-withdrawing substituent at the α-position in indolines greatly increased the diastereoselectivity of the amine products, and the corresponding products **4Id**–**4Kd** were obtained with excellent levels of diastereoselectivity (up to >20:1) in 94–98% yields (Table 5, entries 9–11). The relative configuration of **4Gm** was determined by X-ray crystallographic analysis (Figure 1).[18] The relative configuration of all other products was determined with reference to **4Gm**.

Mechanistic studies: In recent years, there has been a surge of interest to study the mechanism of gold-catalyzed reactions by DFT calculations.[19] In this work, several mechanistic scenarios were considered for the gold(I)-catalyzed synthesis of tertiary amines from secondary amines and alkynes. Generally, two mechanisms are used to describe hydroami-

Table 5. Gold(I)-catalyzed diastereoselective synthesis of tertiary amines with various aryl alkynes and indolines.[a]



	Indoline	Alkyne	Product	*t* [h]	Yield [%][b]	d.r.[c]
			 (+/-)			
1	R^1 = Me (**1G**)	R^2 = Ph (**2a**)	**4Ga**	17	95	15:1
2	R^1 = Me (**1G**)	R^2 = 4-MeOPh (**2c**)	**4Gc**	9	99	13:1
3	R^1 = Me (**1G**)	R^2 = 3-MeOPh (**2d**)	**4Gd**	24	97	19:1
4	R^1 = Me (**1G**)	R^2 = 2-MeOPh (**2e**)	**4Ge**	9	93	19:1
5	R^1 = Me (**1G**)	R^2 = 4-MePh (**2b**)	**4Gb**	22	90	13:1
6	R^1 = Me (**1G**)	R^2 = 2-MePh (**2m**)	**4Gm**	22	83	15:1
7[d]	R^1 = Me (**1G**)	R^2 = 4-CF_3Ph (**2n**)	**4Gn**	48	93	12:1
			 (+/-)			
8	R^1 = Ph$(CH_2)_2$ (**1H**)	R^2 = 3-MeOPh (**2d**)	**4Hd**	20	92	14:1
9	R^1 = Ph (**1I**)	R^2 = 3-MeOPh (**2d**)	**4Id**	22	98	>20:1
10	R^1 = 4-MePh (**1J**)	R^2 = 3-MeOPh (**2d**)	**4Jd**	20	95	>20:1
11	R^1 = 4-ClPh (**1K**)	R^2 = 3-MeOPh (**2d**)	**4Kd**	18	94	>20:1

[a] Reaction conditions: indoline derivatives (0.5 mmol), alkyne (0.6 mmol), ethyl Hantzsch ester (**3**) (0.75 mmol), [{(tBu)$_2$(o-biphenyl)P}AuCl]/$AgBF_4$ (2 mol%), benzene (2 mL) at room temperature. [b] Isolated yield based on amine. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy; major isomer shown. [d] 5 mol% of [{(tBu)$_2$(o-biphenyl)P}AuCl]/AgOTf was used in the presence of activated, powdered molecular sieves (5 Å MS) at 40 °C.

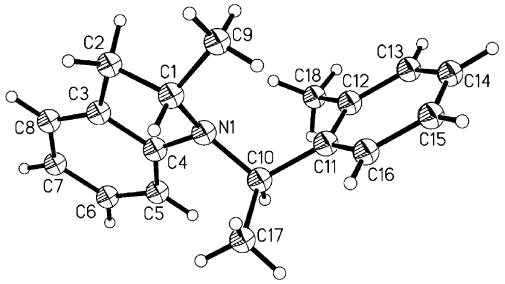
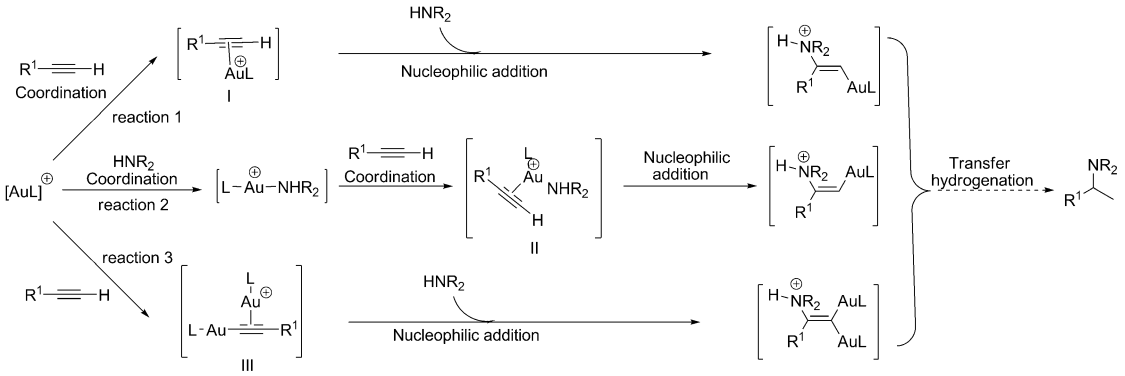


Figure 1. Molecular structure of compound **4Gm**.

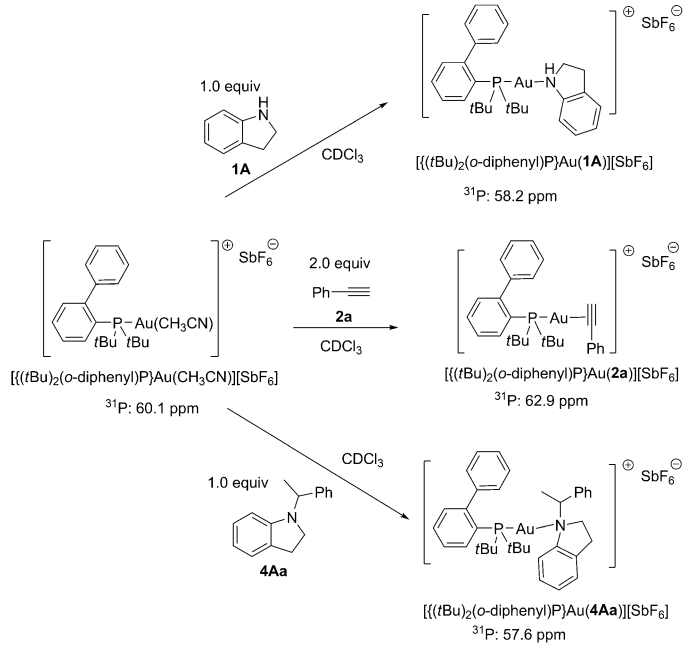
nation of unsaturated C–C bonds catalyzed by transition-metal complexes. One is based on nucleophilic addition of amine to a coordinated unsaturated C–C bond (reaction 1 in Scheme 2), the other involves complexation of both amine functionality and the unsaturated C–C bond with the metal catalyst followed by insertion of the unsaturated C–C bond into the metal–amine bond (reaction 2 in Scheme 2).[20] In the cases of gold(I)-catalyzed hydroamination of alkenes and allenes with less basic amides or carbazates, nucleophilic attack of an amide on a gold(I)-coordinated C–C multiple bond has been proposed (reaction 1 in Scheme 2), which has been supported by experimental and/or computational studies, as reported by Ujaque[21a,b] and Toste.[21c,22] While a mechanism of complexation of both the amine functionality and the unsaturated C–C bond with the gold catalyst through a three-coordinate gold intermediate **II** has been proposed for intermolecular hydroamination involving the more basic simple amines (reaction 2 in Scheme 2),[5b,23] recent investigations by Bertrand and co-workers indicated that gold-catalyzed intramolecular hydroamination of alkynes with simple secondary amines could proceed by means of an alternative reaction pathway involving alkyne activation/nucleophilic attack through an alkyne-coordinated gold intermediate **I** (reaction 1 in Scheme 2).[24] On the other hand, although a monomeric cationic gold(I) complex[25] has been proposed to be the catalytically relevant species for nucleophilic addition of amine to terminal alkyne catalyzed by gold(I) complex, on the basis of conventional reaction mechanism widely proposed for palladium[26] and platinum complexes,[27] several vinyl–gold dimer intermediates **III** (reaction 3 in Scheme 2) derived from gold-mediated addition of nucleophiles to terminal alkynes have been isolated and characterized.[28] Furthermore, Toste and co-workers recently reported experimental and computational evidences for dinuclear gold(I) complexes as key intermediates in gold(I)-catalyzed allenyne cyclization.[29]

According to these recent experimental and computational studies, three possible pathways for the gold(I)-catalyzed tandem reaction of alkynes with basic secondary amines described in this work are depicted in Scheme 2, one of which features activation of the alkyne linkage, whereas the others involve either activation of the amine functionality followed by the coordination of alkyne to form a three-coordinate gold intermediate **II**, or dinuclear gold(I) species **III** as a possible intermediate. In an effort to understand the mechanism of this tandem reaction and to account for the good diastereoselectivity, we have made attempts to detect the reaction intermediate(s) by NMR spectroscopy and ESI-MS; we have also performed isotope-labeling studies and DFT calculations.



Scheme 2. Possible pathways of gold(I)-catalyzed tandem reaction of alkynes with secondary amines.

Identification of reaction intermediate(s) by NMR spectroscopy and ESI-MS: The interaction between the gold(I) catalyst and substrate/product was studied by ^{31}P NMR spectroscopy, because the ^{31}P signal of the phosphine ligand is sensitive to the electronic environment around the gold center.[22,30] Model gold(I) complexes containing alkyne, secondary amine, or tertiary amine moieties were prepared from $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$[31] in CDCl_3 at room temperature (Scheme 3). We found that the ^{31}P signals of the gold(I) complexes containing alkyne, secondary amine, or tertiary amine moieties are significantly different from each other, thus enabling identification of reaction intermediate(s) by ^{31}P NMR spectroscopy. The sample containing $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ and phenylacetylene (**2a**) in a 1:2 ratio showed a ^{31}P NMR signal at $\delta =$ 62.9 ppm. By comparison, the sample containing $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ and indoline (**1A**) in a 1:1 ratio showed a ^{31}P NMR signal at $\delta = 58.2$ ppm, and another sample containing $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ and product **4Aa** in a 1:1 ratio showed a similar ^{31}P NMR signal at $\delta = 57.6$ ppm. However, the ^{31}P NMR signal of $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ alone was observed at $\delta = 60.1$ ppm. Next, the reaction of **1A** with **2a** in the presence of Hantzsch ester (**3**) catalyzed by $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ (10 mol%) in CDCl_3 at room temperature was monitored by ^{31}P NMR spectroscopy (Figure 2). In this experiment, we found that the signal corresponding to $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ ($\delta =$ 60.1 ppm) vanished and a new peak at $\delta = 62.9$ ppm was observed when $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ was added to a reaction mixture of **1A**, **2a**, and **3**. As the reaction progressed to higher conversion (up to 86%), a second peak at $\delta = 57.9$ ppm developed, and this peak is attributed to $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\mathbf{4Aa})]\text{SbF}_6$, because the same ^{31}P signal was observed if mixing just **4Aa** with $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})]\text{SbF}_6$ in CDCl_3 (Scheme 3). The signal at $\delta = 62.9$ ppm observed in the catalytic reaction is consistent with the ^{31}P NMR signal of $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\mathbf{2a})]\text{SbF}_6$, suggesting the possibility of coordination of the alkyne to cationic Au^{I}. The presence of coordinated alkyne intermediate and the absence of gold–amine species in the reaction of **1A** with **2a** in the presence of **3** catalyzed by $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ might be consistent with a mechanism involving nucleophilic attack of secondary amine to a gold(I)-coordinated alkyne. A similar reaction mechanism of hydroamination involving less basic nitrogen nucleophiles had previously been reported by both Toste and Ujaque.[21,22]



Scheme 3. Reactions of phenylacetylene (**2a**), indoline (**1A**) and product **4Aa** with a stoichiometric amount of $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$.

We hypothesized that gold(I)-coordinated enamine may be a key intermediate in this gold(I)-catalyzed tandem reaction of alkynes with amines. To detect the gold(I)-coordinated enamine intermediate, we examined the reaction mixture by electrospray ionization mass spectrometry (ESI-MS). ESI-MS analysis of a solution mixture containing **1A**, **2a** and $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ (20 mol%) in CH_2Cl_2 after stirring for 15 min at room temperature showed a cluster peak at m/z 716.1, attributed to the complex formed between $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}]^+$ and the en-

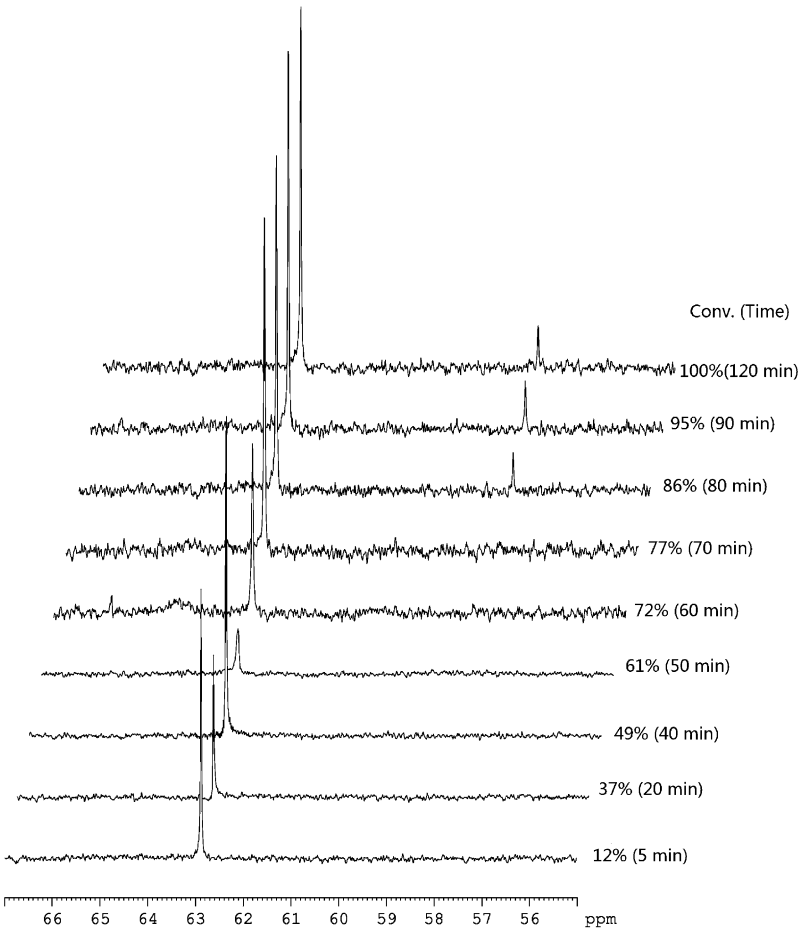


Figure 2. Stacked plots of ^{31}P NMR spectra obtained at various conversions of indoline (**1A**) catalyzed by 10 mol% of $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ in CDCl_3 at room temperature.

amine intermediate generated in situ (Figure 3). The obseved isotopic pattern depicted in Figure 3 matches the calculated pattern well (see the Supporting Information, Figure S5). Collision-induced dissociation of the $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{C}_{16}\text{H}_{15}\text{N})]^+$ ion at *m*/*z* 716.1 resulted in the formation of a new ion at *m*/*z* 494.7, which could be attributed to fragmentation of $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{C}_{16}\text{H}_{15}\text{N})]^+$ into $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}]^+$ apparently by loss of enamine (see the Supporting Information, Figure S6). These data reveal that in the course of this reaction, transfer hydrogenation might proceed via a gold(I)-coordinated enamine intermediate.

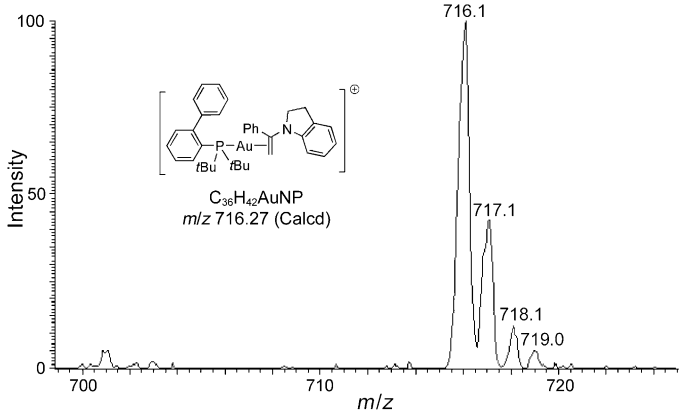
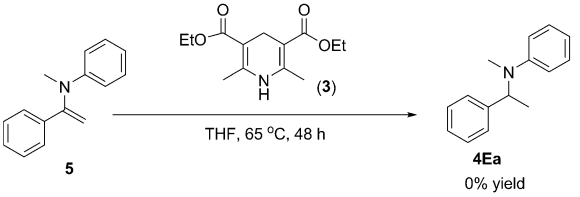


Figure 3. ESI-MS spectrum of a solution containing **1A**, **2a**, and $[(t\text{Bu})_2(o\text{-biphenyl})\text{PAu}(\text{CH}_3\text{CN})][\text{SbF}_6]$ (20 mol%) in CH_2Cl_2 showing a cluster peak at *m*/*z* 716.

Isotope-labeling studies: A series of control experiments were conducted to gain insight into the role of gold catalyst in the hydride reduction step. Since we were not able to isolate the enamine intermediate from the reaction of indoline (**1A**) with phenylacetylene (**2a**), the relatively stable enamine **5** was prepared in order to see whether gold catalyst was crucial for the subsequent transfer hydrogenation reaction [Eqs. (1) and (2)]. For example, in the absence of gold catalyst, product **4Ea** was not obtained for the reaction of enamine **5** in the presence of **3** (1.5 equiv) conducted at 65°C for 48 h [Eq. (1)]. In contrast, we observed that in the presence of $[\{(t\text{Bu})_2(o\text{-biphenyl})\text{P}\}\text{AuCl}]/\text{AgBF}_4$ (5 mol%), the reaction gave the desired product **4Ea** in 84% yield after 24 h at 40°C [Eq. (2)]. We also examined a reaction of **1A** with **2a** in the presence of deuterated Hantzsch ester **6** catalyzed by $[\{(t\text{Bu})_2(o\text{-biphenyl})\text{P}\}\text{AuCl}]/\text{AgBF}_4$ (2 mol%) in benzene at 40°C for 24 h, which gave product **7** in 85% yield with 100% deuterium incorporation at the C-1 position [Eq. (3)]. This implies that one of the hydrides on the carbon atom of Hantzsch ester was completely transferred to the C-1 atom of the enamine intermediate generated in situ from the reaction of alkyne with secondary amine catalyzed by the gold complex.

DFT calculations: To gain a better insight into the reaction intermediate(s) and transition state(s) involved in this



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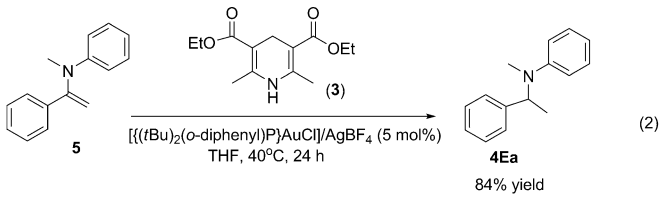
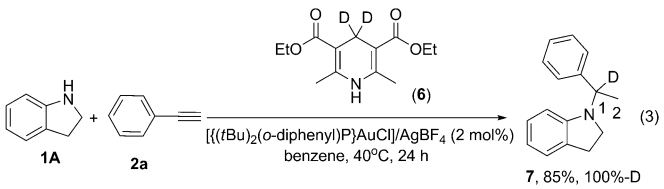
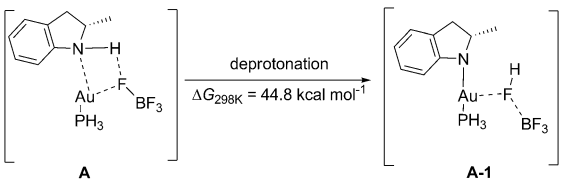




tandem process (Scheme 2), we investigated the reaction mechanism by performing hybrid density functional theory calculations at the B3LYP/6-31G(d) (LANL2DZ for Au) level. In all of the calculations, (*S*)-2-methylindoline and 2-methylphenylacetylene were selected as the substrates to examine the origin of diastereoselectivity. The phosphine ligand PH_3, which had been used as a model of phosphine ligands in a number of computational studies of gold(I)-catalyzed reactions,[19e,21,29] was used instead of (2-biphenyl)di-*tert*-butylphosphine used in our experimental study. The first step of this catalytic tandem process is the coordination of cationic gold catalyst to the reactive functional group of the substrates. In principle, $[Au(PH_3)]^+$ could coordinate to either the nitrogen atom of a more basic secondary amine or C–C triple bond of alkyne.[21–25] Therefore, both gold(I)–amine and gold(I)–alkyne complexes should be considered as the potential catalytic species for gold(I)-catalyzed tandem reactions of alkynes with more basic secondary amines.

Since the metal complex could serve as precatalyst for the formation of a protic acid to subsequently catalyze the addition of secondary amines to alkynes,[21a,32] the deprotonation of gold(I)–amine complex **A** with assistance of counterion BF_4^- for the formation of $[(H_3P)Au(NR_2)]$ and HBF_4 was first considered. All attempts to locate the transition state for the formation of complex **A-1** were unsuccessful, thus prohibiting the evaluation of the real reaction barrier for the formation of $[(H_3P)Au(NR_2)]$ and HBF_4. However, the transformation of **A-1** from **A** is significantly endothermic by 44.8 kcal mol^{-1} (Scheme 4 and Figure S7, in the Supporting Information), revealing that the mechanism through the



Scheme 4. Deprotonation process of gold(I)–amine complex **A**.

deprotonation of gold(I)–amine complex **A** for the formation of $[(H_3P)Au(NR_2)]$ and HBF_4 is unlikely.

As mentioned previously, the alkyne-coordinated gold intermediate **I** and the three-coordinate gold intermediate **II** for the gold(I)-catalyzed hydroamination of alkynes with basic amines have been proposed (Scheme 2).[5b,23] Thus, in this work, two different reaction pathways involving either a monomeric cationic gold(I)–alkyne complex $\mathbf{C_A}$ or a three-coordinate gold(I) complex **B** by complexation of alkyne and secondary amine to gold(I) were investigated. As depicted in Figure 4, the first reaction pathway starts with intermediate **B′** or **B**, in which the Au···N or Au···C bonds for complex **B** or **B′** are weak, as revealed by their long bond lengths of 3.29 and 3.53 Å for **B** and **B′**, respectively (see the Supporting Information, Figure S7). This result does not lend support to a three-coordinate gold(I) intermediate. However, a transition state **B-TS-1** with a free energy of 5.4 kcal mol^{-1} from complex **B** or **B′** was located, which leads to the gold(I)-coordinated enamine **B-1**. Next, the second reaction pathway involving a monomeric cationic gold(I)–alkyne complex $\mathbf{C_A}$ was considered (Figure 4 and Figure S8 in the Supporting Information). The calculation showed that the nucleophilic addition of indoline to gold(I)–activated alkyne $\mathbf{C_A}$ is relatively facile, only requiring an activation free energy of 2.7 kcal mol^{-1} via transition state $\mathbf{C_A}$**-TS-1** to afford the coordinated product $\mathbf{C_A}$**-1**. According to our calculation, transition state $\mathbf{C_A}$**-TS-1** is lower in energy than **B-TS-1** by 2.7 kcal mol^{-1}, suggesting that the hydroamination reaction via the three-coordinate gold(I) intermediate **B** or **B′** is not energetically favored over that via the gold(I)–alkyne intermediate $\mathbf{C_A}$. Also, no spectroscopically detectable interaction between the gold center and secondary amine in the reaction system was revealed by ^{31}P NMR measurements, thereby disfavoring the coordination of amine to the gold catalyst followed by the formation of gold(I)–amine complex **A-1** or three-coordinate gold(I) complex **B** or **B′**. Therefore, in the following reaction pathways, only the pathway(s) of the catalytic tandem reactions starting from gold(I)–alkyne intermediate $\mathbf{C_A}$ was considered.

The subsequent step is a [1,3]-proton-transfer process from a nitrogen atom to a carbon atom to furnish the gold(I)-enamine complex $\mathbf{C_A}$**-2** (Figure 4 and Figure S8 in the Supporting Information). The calculation shows that the pathway of [1,3]-proton transfer, assisted by BF_4^-, is much lower in energy than that of the direct [1,3]-proton transfer from the nitrogen atom to the carbon atom by 28.9 kcal mol^{-1}. This might be attributed to BF_4^- ion acting as a proton shuttle to lower the reaction barrier. This result shows that BF_4^- ion plays a critical role in the [1,3]-proton-transfer step, rendering the gold(I)-catalyzed hydroamination reaction more favorable. The Au–C distance of 2.13 Å in complex $\mathbf{C_A}$**-2** reveals that the phosphinegold(I) moiety still coordinates to the C=C double bond of enamine intermediate generated in situ (Figure S8 in the Supporting Information). Electrospray ionization mass spectrometry analysis of the reaction mixture also lends support to the formation

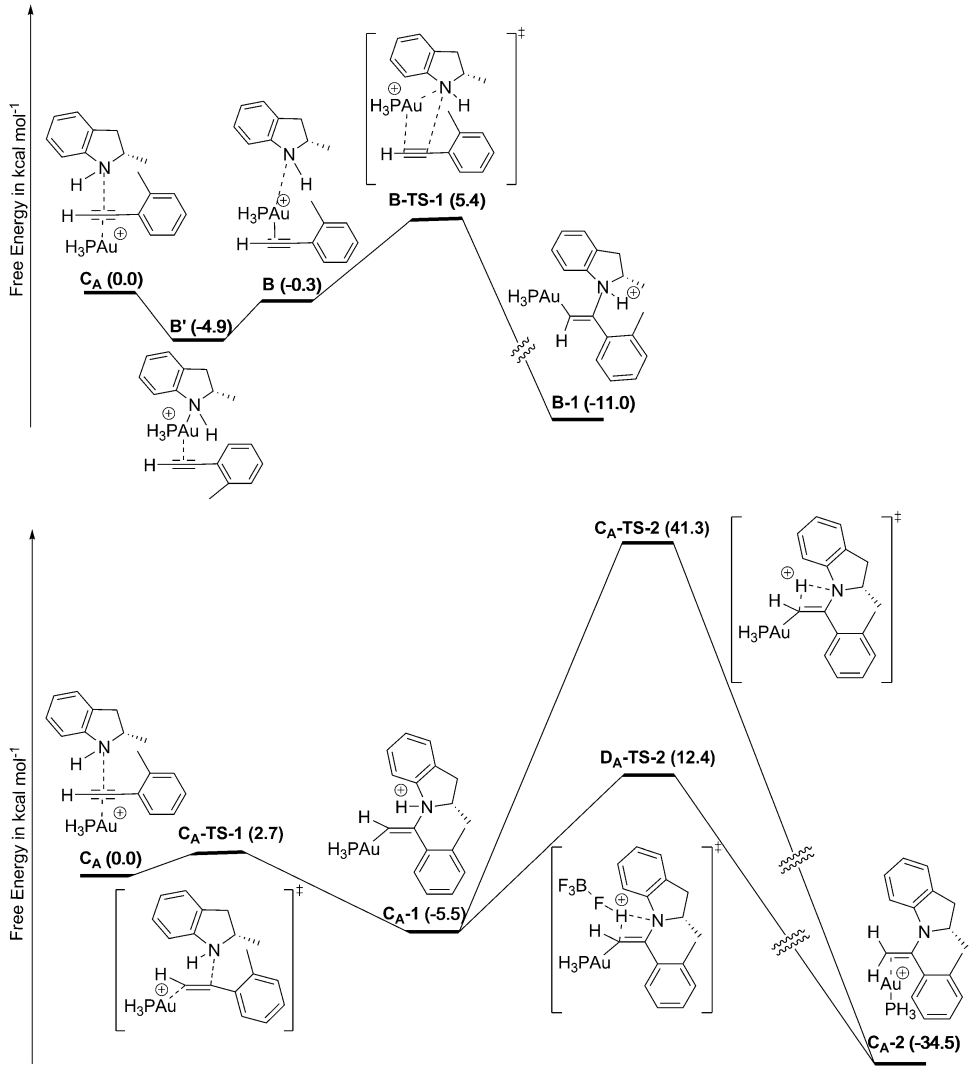


Figure 4. Calculated free energies for intermolecular hydroamination reaction of alkyne with secondary amine by two different reaction pathways using DFT approach at the B3LYP/6-31G(d) (LANL2DZ for Au) level of theory.

of gold(I)-coordinated enamine intermediate (Figure 3), which reacts with a hydride donor to generate tertiary amines.

Since dinuclear gold(I) complex **III** can also act as a key intermediate for gold(I)-catalyzed addition of a nucleophile to a terminal alkyne (Scheme 2),[28,29] this complex should also be considered as a potential intermediate in our catalytic reaction. However, the calculated energy profiles show that the reaction mechanism involving dinuclear gold(I) intermediate is characterized by a high barrier (by 44.8 kcal mol^{-1}, see the Supporting Information, Figure S9 and S10), which is not consistent with the mild reaction conditions. Additionally, internal aryl alkyne **2k** was a suitable substrate for this catalytic tandem reaction under the same reaction conditions (Table 2, entry 11). Furthermore, the hydroamination of internal aryl alkynes with dialkylamine in the presence of a gold(I) complex, recently reported by Stradiotto and co-workers,[5b] also worked well. These experimental and computational findings indicate that a reaction mechanism via a dinuclear gold(I) intermediate is unlikely.

Next, we turned our attention to investigate the subsequent hydrogen-transfer process using HEH as a reducing agent. As stated in previous section, no reaction between enamine **5** and HEH (**3**) was observed in the absence of gold catalyst [Eq. (1)], revealing that the latter plays an important role in the hydride reduction step. Furthermore, there are experimental and computational evidences revealing that the phosphine-gold(I) moiety coordinates to the C–C double bond of an enamine intermediate generated in situ after the intermolecular hydroamination. This leads to increase of electrophilic character of enamines and facilitates the subsequent attack by hydride. Therefore, calculations starting from intermediate **G** for the hydrogen-transfer process were performed; the computed energy profiles and optimized key structures are depicted in Figure 5 and Figure S11 of the Supporting Information. The transition state of **G-TS-1** is stabilized by a C1···H_a···C(HEH) bonding interaction (in which the distances of C1···H_a and H_a···C(HEH) bonds are 1.38 and 1.42 Å, respectively), and by a F···H_b bond through BF_4^- and H_b (on the nitrogen atom of HEH; see the Supporting Information, Figure S11). This is in concordance with the finding from the deuterium incorporation experiment in that the hydride on the carbon atom of HEH is completely transferred to C-1 atom of intermediate **G-1** [Eq. (3)]. The calculated result shows that the hydrogen-transfer process requires an activation energy of 27.1 kcal mol^{-1} and is slightly exergonic by 1.3 kcal mol^{-1}. Finally, the protodemetallation through proton transfer from HEH to complex **G-1** followed by transfer of gold(I) catalyst to another alkyne completes this catalytic tandem cycle.

Based on the experimental findings, we found that the ancillary ligand on gold(I) has little effect on the diastereoselectivity of the corresponding product (Table 4). In contrast, the α-substituent group of indolines plays a key role on the diastereoselectivity (Table 5). To explain the origin of the

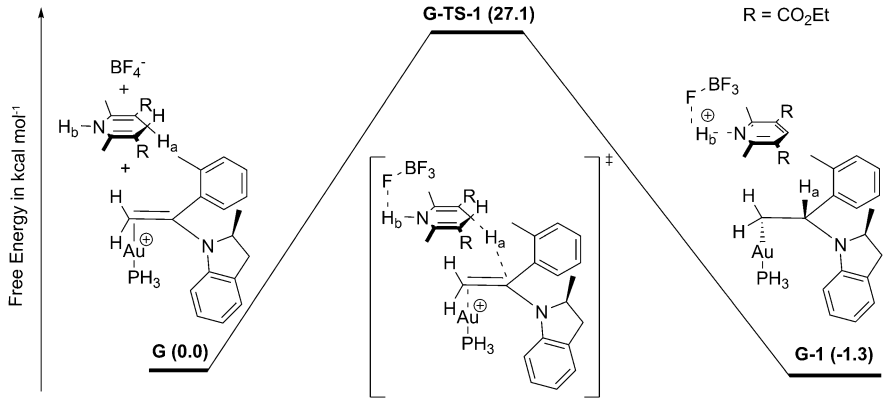
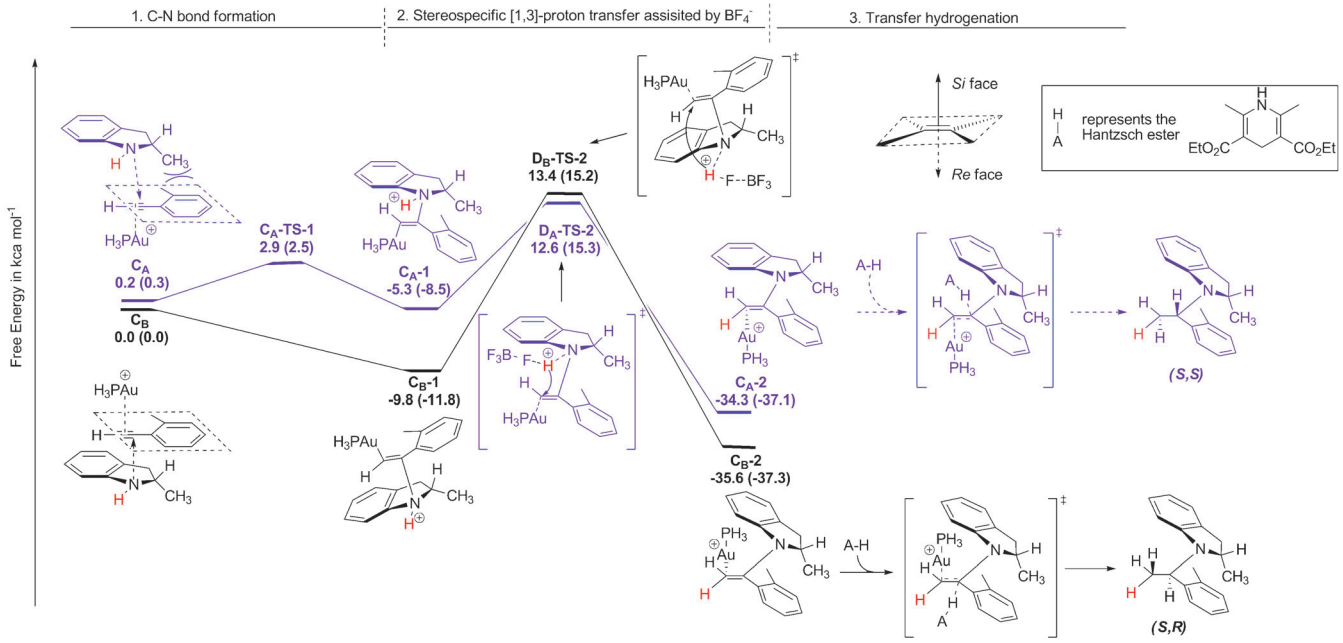


Figure 5. The calculated potential energy surface for transfer hydrogenation of enamine using Hantzsch ester as hydride source via a monomeric, cationic phosphinegold(I) intermediate.

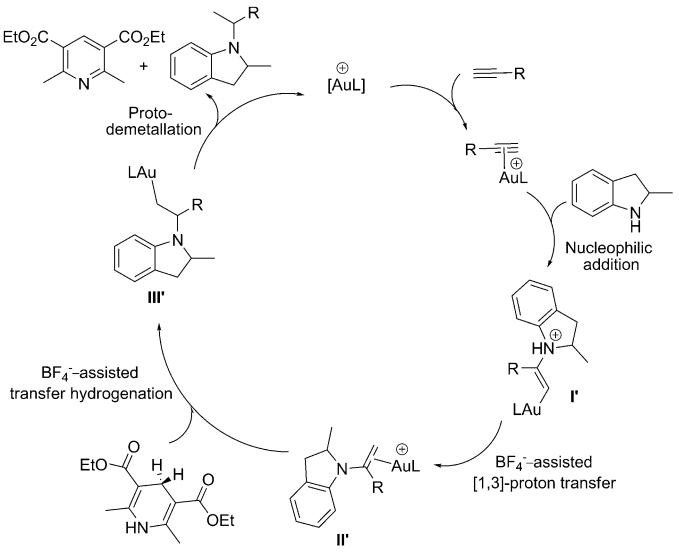
diastereoselectivity of the reaction, two pathways were examined for this tandem reaction of 2-methylphenylacetylene with (*S*)-2-methylindoline through monomeric cationic phosphinegold(I)–alkyne intermediate: path A (route in purple) and path B (route in black) as shown in Scheme 5. In both pathways, the gold(I) complex first catalyzes intermolecular C–N bond formation followed by a stereospecific BF_4^--assisted [1,3]-proton transfer to give gold(I)-coordinated enamine intermediates $\mathbf{C_A}$**-2** and $\mathbf{C_B}$**-2** (Scheme 5 and Figure S8 in the Supporting Information). In these intermediates, the Au complex coordinates to either the *Re* face (for $\mathbf{C_A}$**-2**, route in purple) or the *Si* face (for $\mathbf{C_B}$**-2**, route in black) of C–C double bond of resultant enamine. Hydride transfer of HEH only takes place from the other face of C–C double bond of enamine intermediates (*Si* face for $\mathbf{C_A}$**-2** to give (*S*,*S*)-product and *Re* face for $\mathbf{C_B}$**-2** to give (*S*,*R*)-product, respectively), avoiding steric interactions. For path A, the calculations indicate that the C–N bond formation and BF_4^--assisted [1,3]-proton transfer require free activation energies of 2.9 and 12.6 kcal mol^{-1}, respectively, in the gas phase. In sharp contrast, for path B, all efforts to locate the transition state for the transformation of $\mathbf{C_B}$ to $\mathbf{C_B}$**-1** were unsuccessful, indicating that the C–N bond formation might be barrierless (route in black). Subsequent stereospecific BF_4^--assisted [1,3]-proton transfer has a free energy barrier of 13.4 kcal mol^{-1} in the gas phase. On the other hand, the solvent effect on the reaction energetics for the present two pathways was calculated by CPCM(UAHF) model using the gas-phase geometry obtained from the B3LYP/6-31G(d) (LANL2DZ for Au atom) level with benzene as the solvent. The calculation showed that the potential-energy surface in benzene is similar to that obtained in the gas phase (see ΔG values in Scheme 5). As depicted in Scheme 5, comparison of the potential-energy surfaces reveals that: 1) intermediate $\mathbf{C_B}$**-1** is lower in energy than $\mathbf{C_A}$**-1** (by 4.5 and 3.3 kcal mol^{-1} in the gas phase and benzene, respectively); and the process is potentially barrierless for



Scheme 5. The calculated two reaction paths (path A in purple and path B in black) for hydroamination reaction of 2-methylphenylacetylene with (*S*)-2-methylindoline through a monomeric, cationic phosphinegold(I) catalyst. The free energies of activation (ΔG_{solv} in kcal mol^{-1}) in benzene at the CPCM (UAHF)-B3LYP/6-31G(d) (LANL2DZ for Au) level of theory are in the parentheses.

path B rather than the activation barrier of 2.9 and 2.5 kcal mol^{-1} in the gas phase and in benzene for path A, respectively. 2) Although the BF_4^--assisted [1,3]-proton transfer is rate-limiting for formation of the gold(I)-coordinated enamine intermediates $\mathbf{C_A}$**-2** and $\mathbf{C_B}$**-2**, the reaction barriers for both pathways are marginally different in energy (0.8 and 0.1 kcal mol^{-1} in the gas phase and benzene, respectively). This result indicates that the origin of diastereoselectivity is closely related to the process for C–N bond formation. Therefore, the formation of C–N bond in path B is probably responsible for a preference of (*S*, *R*)-product when (*S*)-2-methylindoline is used as the substrate. It can also be seen that the diastereoselectivity of the reaction is affected by steric interaction between the α-substituent group of indoline and the phenyl group of alkyne, which is also consistent with the experimental findings that the more sterically demanding substrates with the α-substituent group resulted in the products with higher diastereoselectivity (**4Id**–**4Kd**, Table 5).

On the basis of the above NMR, ESI-MS, isotope labeling, and computational studies, we propose a mechanism for this gold(I)-catalyzed tandem reaction, as depicted in Scheme 6. Coordination of an alkyne to the cationic gold(I)



Scheme 6. Proposed reaction pathway.

complex gives a cationic gold(I)–alkyne intermediate. Nucleophilic attack takes place followed by BF_4^--assisted [1,3]-proton transfer to generate gold(I)-coordinated enamine intermediate. Subsequent BF_4^--assisted transfer hydrogenation with HEH, followed by the protodemetallation of intermediate **III′**, affords tertiary amines and regenerates the gold(I) catalyst. The findings from both experimental and computational studies suggest that the first step of this tandem reaction involving a monomeric cationic gold(I)–alkyne intermediate is more likely to occur than a gold(I)–amine intermediate, a three-coordinate gold(I) intermediate, or a dinuclear gold(I)–alkyne intermediate. These studies also support the proposed reaction pathway involving the gold(I)-coordinated enamine complex as a key intermediate for the subsequent transfer hydrogenation with a hydride source.

Conclusion

We have developed an efficient gold(I)-catalyzed tandem hydroamination/transfer hydrogenation of alkynes with secondary amines to furnish tertiary amines in excellent yields and with good to excellent diastereoselectivity. All of these organic transformations can be conducted as a one-pot reaction from simple and readily available starting materials, without the need of isolation of air/moisture-sensitive tertiary enamine intermediates, and under mild reaction conditions (mostly room temperature and mild reducing agents). The procedure is easy to perform and allows for a straightforward, diversity-oriented, and highly diastereoselective synthesis of tertiary amines with a broad substrate scope, thus rendering the method a valuable complementary approach to the conventional synthesis of tertiary amines. To gain mechanistic insight into gold(I)-catalyzed tandem reaction, a comprehensive experimental and computational investigation has been conducted. These studies reveal that a mechanism involves: 1) C–N bond formation through nucleophilic attack of the amine on a monomeric cationic gold(I)–alkyne intermediate; 2) the cleavage of the Au–C bond by means of BF_4^--assisted proton transfer from the amine unit to C=C bond, with subsequent formation of a gold(I)-coordinated enamine intermediate; and 3) transfer hydrogenation of this gold(I)-coordinated enamine intermediate with HEH to give tertiary amine. This mechanistic study has important implications for the understanding of other gold(I)-catalyzed tandem reactions involving the hydroamination step, and future designing of new tandem reactions catalyzed by gold(I) complexes.

Experimental Section

Typical procedure for the gold(I)-catalyzed tandem synthesis of tertiary amines: Amine (0.5 mmol) and alkyne (0.6 mmol), followed by the addition of ethyl Hantzsch ester (0.75 mmol), were added to a mixture of [{(tBu)$_2$(o-biphenyl)P}AuCl] (0.01 mmol) and $AgBF_4$ (0.01 mmol) in dry solvent (2.0 mL) with stirring. The reaction mixture was capped and stirred at RT–60 °C and monitored by TLC. Upon completion of the reaction, the crude product was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 80:1).

Procedure for the [{(tBu)$_2$(o-biphenyl)P}AuCl]/$AgBF_4$-catalyzed reaction of *N*-methyl-*N*-(1-phenylvinyl)aniline (5) with ethyl Hantzsch ester: *N*-Methyl-*N*-(1-phenylvinyl)aniline (**5**) (0.2 mmol) and ethyl Hantzsch ester (0.3 mmol) were added to a mixture of [{(tBu)$_2$(o-biphenyl)P}AuCl] (5 mol %) and $AgBF_4$ (5 mol %) in dry THF (2.0 mL) with stirring. The reaction mixture was capped and stirred at 40 °C for 24 h. The crude reaction mixture was then purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 80:1) to afford the final product **4Ea** (84 % yield) as a clear oil.

Procedure for the isotope studies: Indoline (0.2 mmol) and phenylacetylene (0.24 mmol), followed by deuterated ethyl Hantzsch ester (**6**)

(0.3 mmol), were added to a mixture of [{(tBu)$_2$(o-biphenyl)P}AuCl] (2 mol%) and $AgBF_4$ (2 mol%) in dry benzene (2.0 mL) with stirring. The reaction mixture was capped and stirred at 40 °C for 24 h. The crude reaction mixture was then purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 80:1) to afford the product **7** (85% yield) as a clear oil, which was analyzed using ^{1}H NMR spectroscopy to determine the content of the deuterium incorporation. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 7.36 (m, 5H), 7.06 (m, 2H), 6.63 (t, J = 7.3 Hz, 1H), 6.39 (d, J = 7.8 Hz, 1H), 3.39 (m, 2H), 2.97 (t, J = 8.5 Hz, 2H), 1.56 ppm (s, 3H).

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