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Consecutive Intramolecular Hydroamination/Asymmetric Transfer Hydrogenation under Relay Catalysis of an Achiral Gold Complex/Chiral Brønsted Acid Binary System

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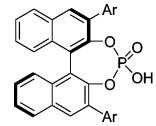
Either metal-based catalysts or organocatalysts are generally used alone to promote fundamentally different reactions in asymmetric catalytic processes.[1] The combination of metal complexes and organic molecules in cooperative and relay catalysis may enable new transformations through the simultaneous or sequential activation and reorganization of multiple chemical bonds by the metal catalysts and organocatalysts. This concept holds great potential for application to a broad scope of organic synthetic reactions, as previously demonstrated by transformations accelerated by metal/organic binary catalyst systems.[2,3] However, relatively few asymmetric protocols gave synthetically useful enantioiselectivity,[2d,f,h−k] and thus the potential of the concept in asymmetric catalysis is poorly understood.

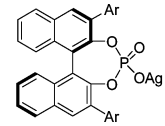
Given their widespread applications as intermediates, building blocks, or reagents in organic synthesis, chiral amines are of increasing commercial importance in fine chemical and pharmaceutical processes. Among numerous synthetic approaches, the enantioselective hydroamination of an unsaturated C−C bond is unarguably the most atom-economic pathway and, hence, is of fundamental significance.[4] Alkynes are more reactive in hydroamination reactions than alkenes.[5] However, hydroamination reactions of alkynes basically generate enamines or imines.[4] An asymmetric catalytic method for the direct transformation of alkynes into amines with high enantiomeric purity is therefore important from a synthetic point of view but has not yet been readily available. Recent reports of elegant sequential processes involving hydroamination of alkynes and a subsequent reduction have transformed alkynes into amines.[6] In these one pot reactions, the reductive reagent was added separately after the hydroamination step, but a low ee was obtained. Herein, we report a novel protocol that directly converted 2-(2-propynyl)aniline derivatives (**1**) into tetrahydroquinolines (**3**) with high *ee in one operation* through consecutive hydroamination of alkynes/asymmetric transfer hydrogenation reactions under the relay catalysis of an achiral Au complex/chiral Brønsted acid binary system.

Our proposed relay catalysis for the conversion of 2-(2-propynyl)anilines **1** into tetrahydroquinolines **3** involves a sequence of reactions initiated by an intramolecular hydroamination catalyzed by an appropriate Au complex,[7] furnishing a 1,4-dihydroquinoline **4**, followed by isomerization of **4** into 3,4-dihydroquinolinium **II** with a chiral Brønsted acid,[8,9] and, ultimately, the asymmetric transfer hydrogenation of the chiral **II**[9] with a Hantzsch ester **2** producing optically active tetrahydroquinoline **3** (Scheme 1). Central to the realization of this strategy would be the identification of a Au complex that would afford an efficient hydroamination but would not affect the Brønsted acid-catalyzed enantioselective transfer hydrogenation. Moreover, appropriate conditions that tolerate either of the two different catalytic reactions are also very important for the proposed relay catalysis.

An initial validation of our hypothesis included a reaction of 2-(3-phenyl-2-propynyl) aniline (**1a**) with Hantzsch ester **2a** using a binary catalyst system consisting of $Ph_3PAuOTf$ (5 mol %), generated *in situ* from Ph_3PAuCl and AgOTf, and Brønsted acid **5** (15 mol %).



5, R = 9-phenanthrenyl

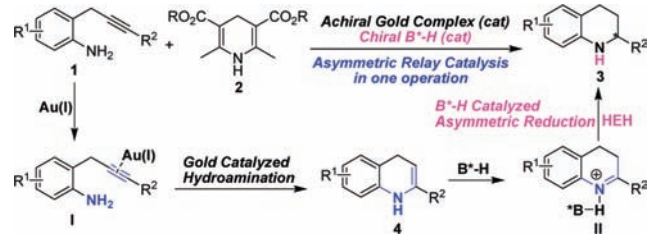


6, R = 9-phenanthrenyl

Gratifyingly, the reaction proceeded cleanly and afforded 2-phenyltetrahydroquinoline **3a** in 98% yield with 92% *ee* (Table 1, entry 1). A control experiment in the presence of 5 mol % of $Ph_3PAuOTf$ led to an incomplete reaction, giving racemic **3a** in low yield (entry 2). The use of $HAuCl_4$ as the collaborator with **5** provided poor enantioselectivity (18% *ee*, entry 3), presumably due to a nonenantioselective transfer hydrogenation accelerated by the proton of $HAuCl_4$ competing with that of **5**, which significantly eroded the stereoselectivity. Significantly, Ph_3PAuCH_3 was found to be the best partner of **5** and provided 97% yield and 97% *ee* for **3a** (entry 4). Tuning the ratio of the phosphoric acid **5** to Ph_3PAuCH_3 had little effect on the stereoselectivity (entries 4−6), although the reaction slowed when the ratio was varied from 3/1 to 1/1 (entry 4 vs 6). This finding demonstrated that the phosphoric acid participated in the second catalysis by activating the imines formed from the hydroamination catalyzed by Au. In the previous work, Ph_3PAuCH_3 reacted with some strong Brønsted acid to form a chiral cationic Au(I) complex,[7c] which might afford the enantioselective sequential reactions by use of its chiral counterion to control the stereochemistry.[10] Thus, we conducted a control reaction exploiting pure chiral gold phosphorate, derived from **6** and Ph_3PAuCl, as the catalyst.[10a] However, the reaction with gold phosphorate was incomplete, with a lower enantioselectivity in comparison with the binary system (entry 7 vs 4). These outcomes indicated that the gold phosphorate, even if it was formed, had little influence on the enantioselective transfer hydrogenation. Instead, the phosphoric acid really controlled the stereochemistry. An examination of other reaction parameters, including solvent and different Hantzsch esters, revealed that toluene was a suitable medium and that **2a** was the best hydride source (entries 8−13). Notably, reducing the catalyst loading still provided high yield and enantioselectivity in a prolonged reaction time (entries 14−15).

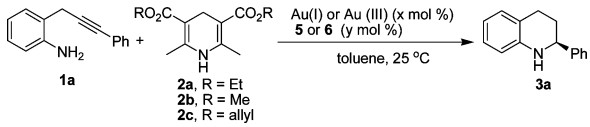
Under the optimized reaction conditions, we investigated the generality of the protocol for 2-(2-propynyl)aniline derivatives

Scheme 1. Relay Catalysis by a Gold Complex/Chiral Brønsted Acid Binary System in Consecutive Intramolecular Hydroamination/Asymmetric Transfer Hydrogenation



10.1021/ja903547q CCC: $40.75

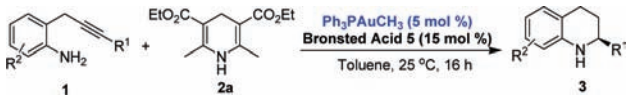
Table 1. Evaluation of Gold Complexes and Optimization of Reaction Conditions

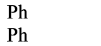


entry	Au (*x* mol %)	**5** or **6** (*y* mol %)	time (h)	yield[b] (%)	*ee*[c] (%)
1	$Ph_3PAuCl/AgOTf$ (5)	**5** (15)	16	98	92[d]
2	$Ph_3PAuCl/AgOTf$ (5)	0	16	<40	0[d]
3	$HAuCl_4 \cdot 4H_2O$ (5)	**5** (15)	16	78	18[d,g]
4	Ph_3PAuMe (5)	**5** (15)	11	97	97
5	Ph_3PAuMe (5)	**5** (20)	12	98	97
6	Ph_3PAuMe (5)	**5** (5)	80	90	97
7	Ph_3PAuCl (5)	**6** (5)	80	35	90
8	Ph_3PAuMe (5)	**5** (15)	14	91	95[e]
9	Ph_3PAuMe (5)	**5** (15)	14	85	96[f]
10	Ph_3PAuMe (5)	**5** (15)	14	88	75[g]
11	Ph_3PAuMe (5)	**5** (15)	14	78	91[h]
12	Ph_3PAuMe (5)	**5** (15)	14	99	94[i]
13	Ph_3PAuMe (5)	**5** (15)	14	99	95[j]
14	Ph_3PAuMe (2)	**5** (6)	32	98	96[d]
15	Ph_3PAuMe (1)	**5** (3)	32	96	97[d]

[a] Unless indicated otherwise, the reaction of **1a** (0.1 mmol) and Hantzsch ester **2a** was carried out in toluene at room temperature. [b] Isolated yield. [c] The *ee* was determined by HPLC. [d] 0.2 mmol **1a** used. [e] In CH_2Cl_2. [f] In $CHCl_3$. [g] In CH_3CN. [h] In THF. [i] Using **2b** as hydride source. [j] Using **2c** as hydride source.

Table 2. Generality for 2-(2-Propynyl)aniline Derivatives



entry	**3**	R^1	R^2	yield (%)[b]	*ee* (%)[c]
1	**3b**	4-MeC_6H_4	H	99	98
2	**3c**	3-MeC_6H_4	H	99	94
3	**3d**	4-BrC_6H_4	H	99	>99
4	**3e**	4-FC_6H_4	H	>99	99
5	**3f**	4-$MeOC_6H_4$	H	>99	98
6	**3g**	2-naphthyl	H	99	99
7	**3h**	2-MeC_6H_4	H	85	94
8	**3i**	4-$CF_3C_6H_4$	H	82	>99
9	**3j**		H	98	87
10	**3k**		H	94	88
11	**3l**	Ph	4,5-(OCH_2O)	96	91
12	**3m**	Ph	4-Ph	>99	95
13	**3n**	Ph	4-F	95	98
14	**3o**	Ph	4-Cl	>99	97
15	**3p**	Ph	5-Cl	>99	90
16	**3q**	Ph	Benzo[g]	94	97[d]

[a] Unless indicated otherwise, the reaction of **1** (0.1 mmol) and Hantzsch ester **2a** was carried out in toluene at room temperature. [b] Isolated yield. [c] The *ee* was determined by HPLC. [d] The reaction was performed for 27 h.

(Table 2). The relay catalytic reaction tolerated a wide spectrum of 2-(2-propynyl)anilines bearing either aromatic or aliphatic substituents on the propynyl moiety (entries 1−10). 2-(3-Aryl-2-propynyl)anilines cleanly underwent the sequential intramolecular hydroamination of alkynes/asymmetric transfer hydrogenation reactions to furnish tetrahydroquinolines in high yields (82−>99%) with excellent enantioselectivity ranging from 94% to >99% *ee* (entries 1−8). Moreover, 2-(3-alkyl-2-propynyl)anilines provided high yields and enantiomeric excesses for the desired products (entries 9 and 10). Importantly, the variation of substituent on the aniline moiety was also tolerable (entries 11−16). Electron-withdrawing, neutral, or electron-donating substituents were well tolerated, providing excellent conversions (94−>99% yields) and stereochemical outcomes (90−98% *ee*). The stereoselectivity is sensitive to the position of the substituent when comparing the reactions producing **3o** and **3p** (entries 14 and 15).

In summary, we have developed an unprecedented protocol which directly transformed 2-(2-propynyl)aniline derivatives into tetrahydroquinolines in one operation with excellent enantioselectivity under the relay catalysis of an achiral Au complex and a chiral phosphoric acid. This reaction was considered a consecutive catalytic process consisting of a Au-catalyzed intramolecular hydroamination of a C−C triple bond and a Brønsted acid catalyzed enantioselective transfer hydrogenation. This work not only provides a new entry to tetrahydroquinolines complementary to the known asymmetric hydrogenation reactions of quinolines[9,11] but also suggests a powerful strategy applicable to the design of transformations beyond the scope of those afforded by either Au complexes[12] or Brønsted acids[13] alone.

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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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