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Hybrid System of Metal/Brønsted Acid Relay Catalysis for the Intramolecular Double Hydroarylation and Cationic Cyclization of Diyne Diethers and Diamines

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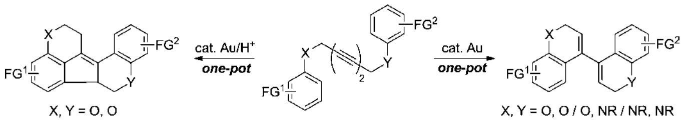
ABSTRACT



We have developed a hybrid system of metal/Brønsted acid relay catalysis for the intramolecular double hydroarylation and cationic cyclization of diyne diethers and diamines to give 4,4′-bi(2*H*-chromene), bi(2*H*-quinoline), and dioxafluoranthenes starting from 2,4-diyne-1,6-diethers and diamines in one reaction vessel under mild conditions.

Transition metal catalyzed intramolecular hydroarylation of alkynes, alkenes, and allenes by the addition of an aryl C−H bond across a π-bond has received considerable attention for its highly useful synthetic applications.[1] This reaction has been demonstrated to be one of the most effective green chemistry methods because of its ideal atom economy.[2] Since the Pd-catalyzed intramolecular hydroarylation of alkynes was first described by Fujiwara,[3] a wide range of transition metal[4] and Lewis acid catalyzed[5] hydroarylations were reported.[6] Recently, we developed Pt-catalyzed hydroarylation of benzyl allenes through a

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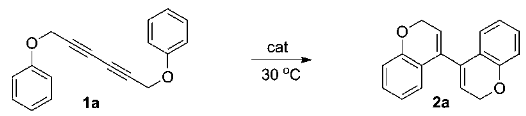
6-*endo* mode for the preparation of 1,4-dihydronaphthalenes.[7] Because tandem reactions have long been established as efficient methods for the rapid synthesis of complex compounds in relatively short steps starting from simple and readily available substrates,[8] we envisioned that a tandem process involving transition metal catalyzed intramolecular hydroarylation of diyne diether and diamine followed by Brønsted acid catalyzed cationic cyclization of diene in one pot would provide structurally diverse heterocycles. Herein, we describe the development of intramolecular Au-catalyzed double hydroarylation of 2,4-diyne-1,6-diethers or diamines followed by cationic cyclization in one pot.

Table 1. Optimization of Intramolecular Catalytic Double Hydroarylation[a]



entry	cat (mol %)	solvent	time (h)	yield (%)[b]
1	$AuCl_3$ (5)/AgOTf (15)	toluene	4	0
2	AuCl (5)/AgOTf (5)	toluene	4	0
3	Ph_3PAuCl (5)/AgOTf (5)	toluene	2	80
4	Ph_3PAuCl (5)/AgOTf (5)	CH_2Cl_2	0.3	90
5	Ph_3PAuCl (5)/$AgBF_4$ (5)	CH_2Cl_2	1	84
6	Ph_3PAuCl (5)/$AgNTf_2$ (5)	CH_2Cl_2	0.3	90
7	Ph_3PAuCl (5)/$AgAsF_6$ (5)	CH_2Cl_2	0.3	88
8	Ph_3PAuCl (5)/$AgSbF_6$ (5)	CH_2Cl_2	0.3	95
9	Ph_3PAuCl (2.5)/$AgSbF_6$ (2.5)	CH_2Cl_2	0.3	90
10	$AgSbF_6$ (5)	CH_2Cl_2	18	0
11	AgOTf (5)	CH_2Cl_2	4	0
12	TfOH (5)	CH_2Cl_2	24	0
13	TfOH (30)	CH_2Cl_2	24	0

[a] Reactions were carried out with **1a** (0.2 mmol) in the presence of catalyst. [b] Isolated yield.

At the outset of our studies, we attempted to optimize the reaction conditions for the intramolecular Au-catalyzed double hydroarylation reaction of 1,6-diphenoxy-2,4-hexadiyne (**1a**) readily prepared by Cu-catalyzed oxidative coupling of phenyl propargyl ether (Table 1).[9] When **1a** was treated with $AuCl_3$ or AuCl (5 mol % each) in the presence of AgOTf (5 mol %) in toluene at 30 °C, the desired reaction did not proceed (entries 1 and 2). However, the use of Ph_3PAuCl and AgOTf (5 mol % each) produced the intramolecular double hydroarylated product **2a** in 80% yield in toluene at 30 °C after 2 h (entry 3). The structure of **2a** was unambiguously determined by spectroscopy. Dichloromethane was found to be the most optimal solvent to give a 90% product yield within 0.3 h at the same temperature (entry 4). Although the employment of $AgBF_4$ (5 mol %) gave **2a** in 84% yield at 30 °C for 1 h (entry 5), $AgNTf_2$ and $AgAsF_6$ (5 mol % each) afforded **2a** in 90% and 88% yields, respectively, after 0.3 h (entries 6 and 7). Ph_3PAuCl and $AgSbF_6$ (5 mol % each) provided **2a** in 95% yield in dichloromethane at 30 °C for 0.3 h (entry 8). The best result was obtained with Ph_3PAuCl and $AgSbF_6$ (2.5 mol % each), producing **2a** in 90% yield (entry 9). Independent use of Ag salt ($AgSbF_6$ and AgOTf, 5 mol % each) without Ph_3PAuCl did not give **2a** (entries 10 and 11). To check the possibility of catalysis by a protic acid, we attempted the double hydroarylation reaction in the presence of trifluoromethanesulfonic acid (5 mol % and 30 mol %) in dichloromethane at rt. Under these conditions, the reaction did not proceed (entries 12 and 13).

To explore the scope of the present tandem hydroarylation with respect to diyne diether and diamine **1**, we carried out further reactions in dichloromethane with Ph_3PAuCl and $AgSbF_6$ (2.5 mol % each, Scheme 1). Varying the electron demand of the substituents on the phenyl ring did not diminish the efficiency of the tandem hydroarylation reaction. Under the optimized reaction conditions, treatment of 1,6-di(3,5-dimethylphenoxy)-2,4-hexadiyne **1b** with the Au-catalyst gave **2b** in 83% yield in 20 min. The tandem cyclization of 1,6-di(4-*tert*-butylphenoxy)-2,4-hexadiyne **1c** proceeded efficiently to provide **2c** in 89% yield in dichloromethane at 30 °C for 30 min. The presence of a 4- and 3-methoxy group on the phenyl ring had little effect on either the reaction rate (30 min) or the product yield (**2d**, 81% and **2e**, 80% yield). When 1,6-diphenoxy-2,4-hexadiyne **1f** having an *N*-Boc amino group was subjected to the reaction conditions, the corresponding hydroarylated product **2f** was obtained in 86% yield albeit with a longer reaction time (7 h). 1,6-Di(2-phenylphenoxy)-2,4-hexadiyne **1g** underwent the Au-catalyzed double hydroarylation reaction, producing **2g** in 92% yield for 30 min. Certain labile functional groups commonly employed in organic synthesis such as bromo or iodo moieties substituted on the phenyl ring were tolerated under these reaction conditions. The presence of a strong electron-withdrawing group such as 4-acetyl and 4-ethoxycarbonyl had little effect on the product yield (**2k**, 88% and **2l**, 91%) although the reaction rate was found to be decreased to some extent. Encouraged by these results, we carried out an intramolecular Au-catalyzed double hydroarylation reaction of diyne diamines. We were pleased to find that substrates derived from *N*-sulfonyl substituted anilines were successfully applied to the cyclization conditions, thus greatly expanding the scope of our synthetic method. For example, when bis(*N*-phenyl-*N*-tosyl)hexa-2,4-diynyl-1,6-diamine (**1m**) was subjected to the optimized conditions, the desired product (**2m**) was obtained in 84% yield albeit requiring a longer reaction time when compared to

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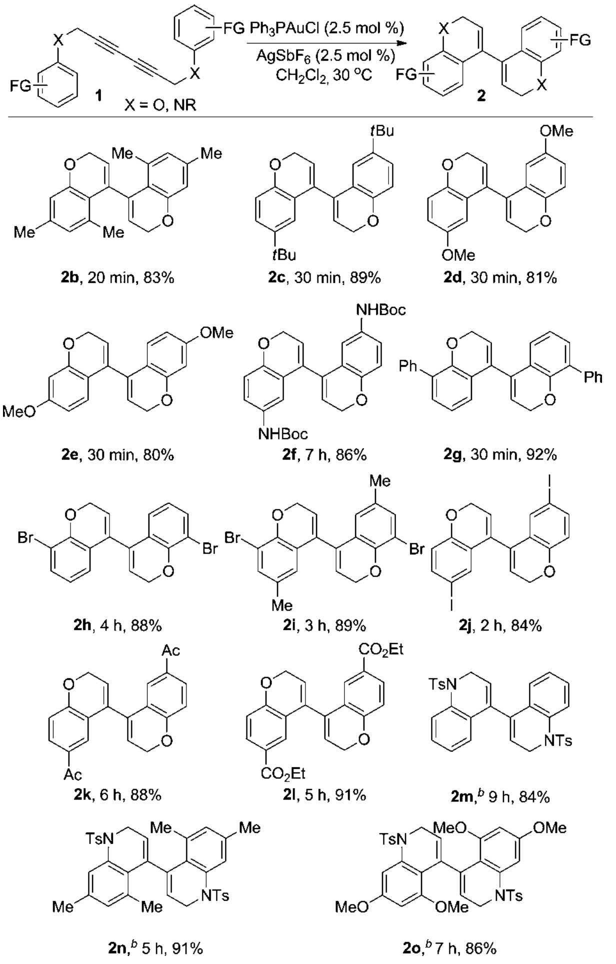
Scheme 1. Intramolecular Au-Catalyzed Double Hydroarylation of Dialkynyl Diethers[a]



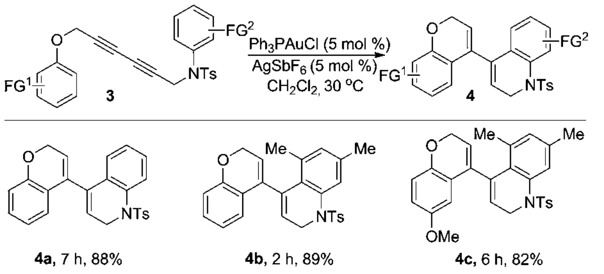
[a] Reactions were carried out with **1** (0.2 mmol) in the presence of catalyst. Percentage indicates isolated yield. [b] Ph_3PAuCl and $AgSbF_6$ (5 mol % each) was used as a catalyst.

substrates bearing an aryl ether unit. The structure of **2m** was unambiguously characterized by a X-ray crystallography.[10] Likewise, bi-(2*H*-quinoline) (**2n** and **2o**) could be obtained in high yields under the same conditions.

We were pleased to find that diyne **3a** having both an ether and amine functional group underwent the desired reaction with Ph_3PAuCl and $AgSbF_6$ (5 mol % each) in dichloromethane at 30 °C, producing the corresponding cyclic compound **4a** in 88% yield through an intramolecular double hydroarylation reaction (Scheme 2). Moreover, under the optimum reaction conditions, diynes **3b** and **3c** bearing mutually different substituents on each phenyl ring were smoothly converted to the cyclic compounds (**4b** and **4c**) in 89% and 82% yields, respectively.

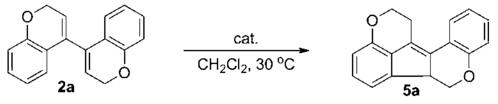
Next, we envisioned that 1,3-dienes **2** might be further cyclized by either a Au or Brønsted acid catalyst, producing dioxafluoranthene. Moreover, if this catalytic cationic cyclization could be accomplished, we envisaged that the cascade reaction consisting of an intramolecular double hydroarylation and a cationic cyclization might occur in one pot. Unfortunately, the subsequent cyclization reaction of **2a** with Ph_3PAuCl and $AgSbF_6$ (2.5 mol % each) in dichloromethane did not proceed (Table 2, entry 1). Although exposure of **2a** to trifluoromethanesulfonic acid (TfOH, 5 mol %) afforded **5a** in 3% yield (entry 2), we were delighted to observe that TfOH (30 mol %) gave the cationic cyclized product **5a** in 80% yield in dichloromethane at 30 °C for 0.5 h (entry 3). The fact that intramolecular double hydroarylation proceeds only with a Au catalyst (Table 1, entry 9 vs 13) and the cationic cyclization of its product **2a** is just achieved by TfOH catalyst (Table 2, entry 1 vs 3) indicates that these two types of cyclization reactions could be combined as a cascade reaction in one pot. Although subjecting **1a** to the optimum conditions in the presence of TfOH (10 and 20 mol %) gave the desired product **5a** in 15% and 49% yields, respectively, the second reaction, cationic cyclization of 1,3-diene **2a**, was not completed (Table 3, entries 1 and 2). However, when **1a** was treated with Ph_3PAuCl and $AgSbF_6$ (2.5 mol % each) in the presence of TfOH (30 mol %), the cascade reaction consisting of a Au-catalyzed intramolecular double hydroarylation and cationic cyclization proceeded smoothly without the interference of two types of catalyst, producing **5a** in 79% yield in dichloromethane at 30 °C for 2 h in one pot (entry 3).

Scheme 2. Intramolecular Au-Catalyzed Double Hydroarylation of **3**[a]



[a] Reactions were carried out with **3** (0.2 mmol) in the presence of catalyst. Percentage indicates isolated yield.

Table 2. Cationic Cyclization of 1,3-Dienes[a]



entry	cat. (mol %)	time (h)	yield (%)[b]
1	Ph_3PAuCl (2.5)/$AgSbF_6$(2.5)	10	0
2	TfOH (5)	12	3
3	TfOH (30)	0.5	80

[a] Reactions were carried out with **2a** (0.2 mmol) in the presence of catalyst. [b] Isolated yield.

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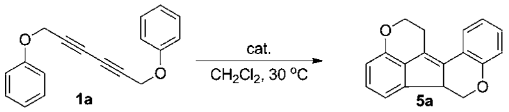
(10) Supporting Information.

Table 3. Double Hydroarylation and Cationic Cyclization of 1,3-Diynes[a]



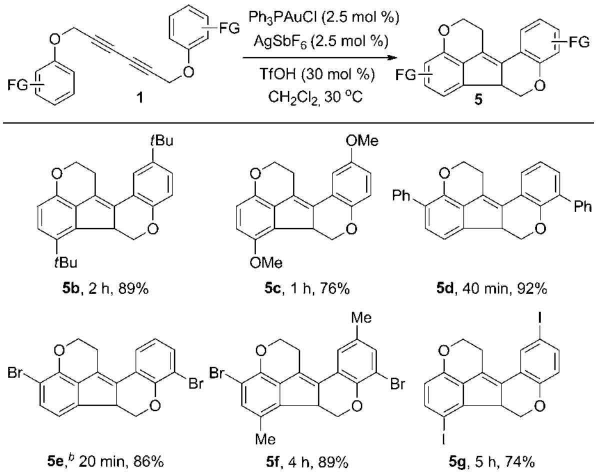
entry	cat. (mol %)	time (h)	yield (%)[b]
1	Ph_3PAuCl (2.5)/$AgSbF_6$ (2.5)/TfOH (10)	24	15 (68)[c]
2	Ph_3PAuCl (2.5)/$AgSbF_6$ (2.5)TfOH (20)	8	49 (28)[c]
3	Ph_3PAuCl (2.5)/$AgSbF_6$ (2.5)/TfOH (30)	2	79

[a] Reactions were carried out with **1a** (0.2 mmol) in the presence of catalyst. [b] Isolated yield. [c] Isolated yield of **2a**.

We next investigated the scope and functional group tolerance of the above double hydroarylation followed by cationic cyclization (Scheme 3). Treatment of **1b** with Ph_3PAuCl and $AgSbF_6$ (2.5 mol % each) in the presence of TfOH (30 mol %) gave the desired product **5b** in 89% yield in dichloromethane at 30 °C for 2 h. Under the optimum reaction conditions, the tandem reaction performed equally well with diynes **1c** and **1d** having a methoxy and phenyl group, producing **5c** and **5d** in 76% and 92% yields, respectively. Treatment of 1,6-di(2-bromophenoxy)-2,4-hexadiyne (**1e**) with Ph_3PAuCl and $AgSbF_6$ (5 mol % each) in the presence of 30 mol % TfOH afforded **5e** in 86% yield. The reaction of **1f** with a Au-catalyst followed by TfOH produced **5f** in 89% yield. 1,6-Di(4-iodophenoxy)-2,4-hexadiyne (**1g**) underwent the tandem reaction to afford **5g** in 74% yield under the present conditions. However, in the case of substrates (**2f**, **2m**, **2n**, and **2o**) having a nitrogen atom, the cationic cyclization of 1,3-diene in the cascade reaction did not proceed after intramolecular Au-catalyzed double hydroarylation.

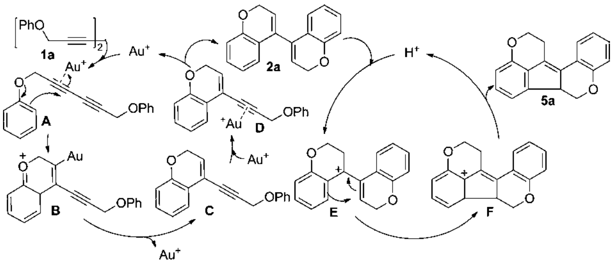
Although the mechanism of the present reaction has not been fully established at the present stage, a possible reaction pathway is shown in Scheme 4. Coordination of a gold catalyst to triple bond in diyne diether **1a** results in the formation of the intermediate **A** which, upon nucleophilic attack of the carbon on the aromatic ring, is cyclized leading to a σ-gold complex **B**. Subsequent aromatization followed by protodeauration of **B** might afford the chromene derivative **C** to release the gold catalyst back into the catalytic cycle. The repeated intramolecular hydroarylation of intermediate **C** with a Au-catalyst would give double hydroarylation product **2a**. 1,3-Diene **2a** is expected to be protonated to produce tertiary benzylic carbocation **E**, and then, an electrocyclization process followed by aromatization finally will furnish **5a**.

Scheme 3. Intramolecular Au-Catalyzed Double Hydroarylation and Cationic Cyclization of Dialkynyl Diethers[a]



[a] Reactions were carried out with **1** (0.2 mmol) in the presence of catalyst. Percentage indicates isolated yield. [b] Ph_3PAuCl and $AgSbF_6$ (5 mol % each) was used as a catalyst.

Scheme 4. Plausible Mechanism



In conclusion, we presented herein the development of Au-catalyzed intramolecular double hydroarylation followed by cationic cyclization that allows the rapid synthesis of 4,4′-bi(2*H*-chromene), bi(2*H*-quinoline), and dioxafluoranthene starting from 2,4-diyne-1,6-diether and diamine in one reaction vessel.

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Supporting Information Available. Experimental procedure and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.