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Concise Synthesis of 1,2-Dihydroisoquinolines and 1*H*-Isochromenes by Carbophilic Lewis Acid-Catalyzed Tandem Nucleophilic Addition and Cyclization of 2-(1-Alkynyl)arylaldimines and 2-(1-Alkynyl)arylaldehydes

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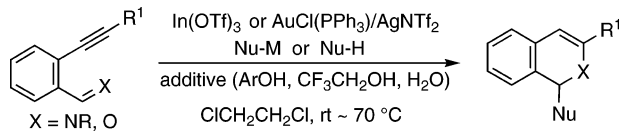

By using carbophilic Lewis acids, $In(OTf)_3$, $NiCl_2$, and $AuCl(PPh_3)/AgNTf_2$, a concise and efficient synthesis of 1,3-disubstituted 1,2-dihydroisoquinolines has been achieved via tandem nucleophilic addition and cyclization of 2-(1-alkynyl)arylaldimines. Addition of proton sources such as water, CF_3CH_2OH, and 2,6-di-*tert*-butyl-4-methoxyphenol was essential for the Lewis acid-catalyzed tandem reactions with organometallic reagents. By switching these catalysts, various types of nucleophiles such as allylstannanes, silyl enol ethers, alkenylboronic acids, and active methylene compounds could be introduced at the C_1 position of 1,2-dihydroisoquinolines in this transformation. Furthermore, this method proved to be applicable to the synthesis of 1*H*-isochromene derivatives via the same tandem reaction of 2-(1-alkynyl)-arylaldehydes.

Introduction

Dihydroisoquinoline is an important and useful skeleton in organic synthesis. Indeed, many total syntheses of natural alkaloids have been achieved using 1,2-dihydroisoquinolines as synthetic intermediates.[1] A number of elegant approaches to the synthesis of 1,2-dihydroisoquinolines has been developed. The Reissert-type reaction of isoquinoline derivatives is one of the methods for 1-substituted 1,2-dihydroisoquinolines,[2] and recently, its asymmetric versions have been keenly investigated.[3] In contrast to 1-substituted 1,2-dihydroisoquinolines, there are only a few convenient methods for 3- and 4-substituted 1,2-dihydroisoquinolines because most of the reported syntheses of the target compounds require multiple steps.[4] Therefore, many synthetic problems still remain to be solved. To overcome the lack of synthetic methods and knowledge, considerable effort has been directed toward the development of concise and efficient syntheses of these compounds using a wide range of transition-metal catalysts.

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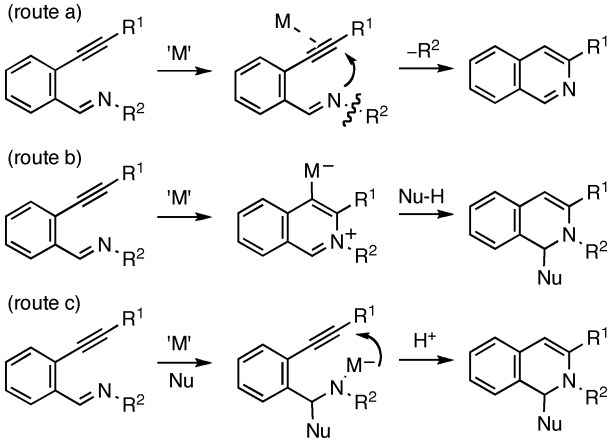
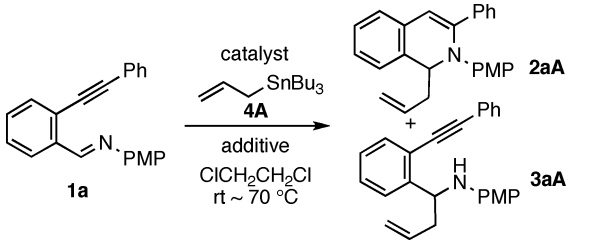
SCHEME 1. Synthesis of Isoquinolines and 1,2-Dihydroisoquinolines from 2(1-Alkynyl)arylaldimines



Recently, transition-metal-catalyzed 6-*endo*-mode cyclizations of 2-(1-alkynyl)arylaldimine (Scheme 1) were discovered as powerful synthetic tools of isoquinolines and 1,2-dihydroisoquinolines, and they were also successfully applied to the total synthesis of natural products.[5] Namely, Larock found that the dealkylative addition of *tert*-butylimine to a C≡C triple bond proceeded cleanly in the presence of a Pd(0) catalyst to give 3-substituted or 3,4-disubstituted isoquinolines (route a).[5a,b] In addition, the Ag(I)- and Pd(II)/Cu(II)-promoted cyclization of 2-alkynylarylimines accompanied by intermolecular nucleophilic addition was developed by Yamamoto's group for the synthesis of 1,3-disubstituted or 1,3,4-trisubstituted 1,2-dihydroisoquinolines (route b).[5c,d] These metallic catalysts probably activated the C≡C triple bond rather than the aldimine moiety. In contrast, quite recently, we have found that the In(III) catalyst, which has both oxophilic and carbophilic characters,[6] effectively activated a C=N double bond[7] and a C≡C triple bond[8] at the same time to obtain the same 1,3-disubstituted 1,2-dihydroisoquinolines via the intermolecular nucleophilic addition to an imine and the subsequent cyclization of the resulting amide to an alkyne[9] (route c). The development of such tandem reactions for the efficient construction of complex molecules is an important goal of organic synthesis from the viewpoints of operational simplicity and assembly efficiency.[10] Herein, we describe the full details[9] of the scope and limitations of Lewis acid-catalyzed tandem nucleophilic addition and cyclization of 2-(1-alkynyl)arylaldimines with a wide range of nucleophiles, together with an extension of the tandem reaction to 2-alkynylarylaldehydes for the synthesis of 1*H*-isochromenes.

TABLE 1. Lewis Acid-Catalyzed Tandem Reaction of 1a with Allyltributylstannane 4A[a]



entry	catalyst	additive[b]	time (h)	yield[c] **2aA** (%)	yield[c] **3aA** (%)
1	$In(OTf)_3$		48	92	0
2	$InBr_3$		60	0	12[d]
3	$Ga(OTf)_3$		48	10	72
4	$Sn(OTf)_3$		60	88	0
5	dry $In(OTf)_3$[e]		48	5	90
6	dry $In(OTf)_3$[e,f]	**A**	48	88	0
7	$NiCl_2$	**B**	48	70	0
8	$PtCl_2$	**B**	48	18	0[d]
9	$AuCl_3$	**B**	48	15	0[d]
10[g]	$AuCl(PPh_3)/AgNTf_2$	**B**	36	72	0
11	$In(OTf)_3$	**B**	48	90	0
12	$In(OTf)_3$	**C**	6	92	0

[a] Reaction of **1a** was carried out with allyltributylstannane **4A** (1.2 equiv) and Lewis acid (0.2 equiv) in 1,2-dichloromethane at 70 °C unless stated otherwise. [b] **A**: H_2O (1 equiv); **B**: CF_3CH_2OH (2 equiv); or **C**: 2,6-di-*tert*-butyl-4-methoxyphenol (2 equiv). [c] Isolated yield. [d] Almost all of **1a** was left in the reaction mixture. [e] Commercially available $In(OTf)_3$ was dried by heating in vacuo before use. [f] 0.1 equiv of $In(OTf)_3$ was used. [g] Reaction was carried out at room temperature.

Results and Discussion

Optimization of Lewis Acids and Proton Sources. We have already reported that the reaction of 2-(1-alkynyl)arylaldimine **1a** with allyltributylstannane **4A** in the presence of 20 mol % $In(OTf)_3$ in 1,2-dichloroethane (DCE) at 70 °C yielded the desired 1,2-dihydroisoquinoline **2aA** in 92% yield after 48 h (Table 1, entry 1). Although in the previous article, mainly In(III) catalysts were examined, due to our interest in indium-mediated reactions,[11] we re-examined the tandem reaction with a wide range of soft or hard Lewis acids to expand their synthetic utility and gain additional insight into this tandem process.

All reactions of **1a** with allyltributylstannane **4A** were carried out under the same reaction conditions except the Lewis acids employed (Table 1, entries 2−9). Use of $InBr_3$ instead of $In(OTf)_3$ provided a small amount of addition product **3aA** (12%) along with recovery of the starting material (entry 2). This result is in sharp contrast to the efficient $InBr_3$-catalyzed cyclization of 2-alkynylanilines to the corresponding indoles.[8d] Considering

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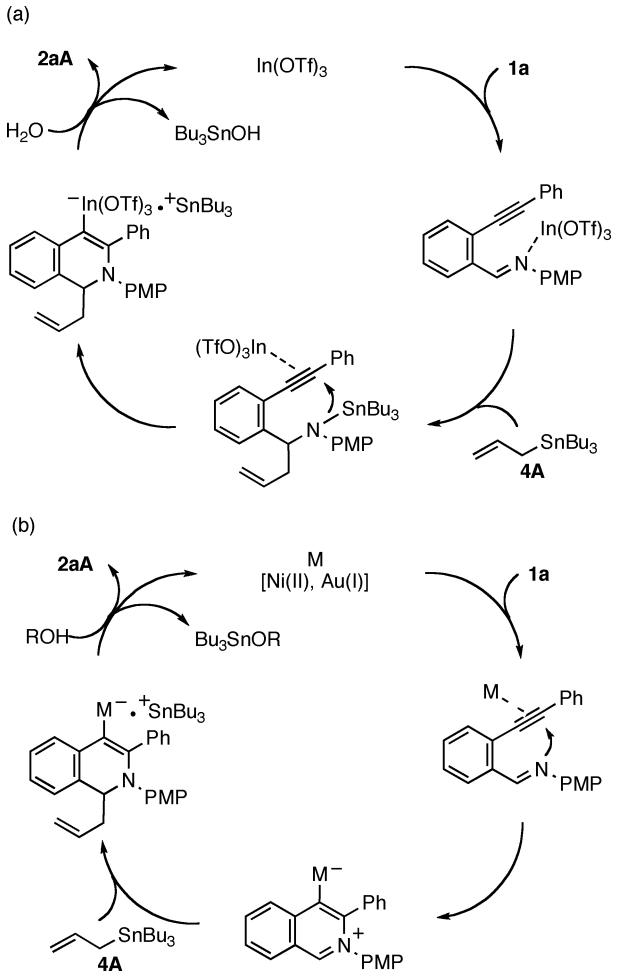
other hard Lewis acids such as $Ga(OTf)_3$ and $Sn(OTf)_2$, each reaction led to a different outcome. When $Ga(OTf)_3$, gallium belonging to the same group 13 metals as indium, was used as the catalyst, **2aA** was obtained as a minor product together with the allylated adduct **3aA** in 72% yield (entry 3). In contrast, the reaction with $Sn(OTf)_2$, tin being a member of group 12 metals, gave the desired cyclic adduct **2aA** as the sole product in 88% yield, although it required a longer reaction time (entry 4). We turned our attention to soft transition-metal catalysts (group 10−and 11 metals) because AgOTf[5d] was only reported to be an effective catalyst for the tandem cyclization of 2-(1-alkynyl)arylaldimines with several active methylene compounds. Then, we explored other carbophilic transition-metal-catalysts, Ni(II) and Pt(II) as group 10 metals[12] and Au(I or III) as a group 11 metal,[13] for the tandem reaction of **1a**. In sharp contrast to the hard metal triflates, these catalysts did not promote the reaction at all, and almost all the starting material was recovered even after 24 h. Since 1 equiv of a proton source is obviously needed as a vinyl proton for this cyclization, these results are reasonable based on the reaction mechanism (see route b in Scheme 1). This indicated that $In(OTf)_3$ might contain a small amount of water, which acted as an appropriate proton source for this tandem reaction. To test this possibility, we tried the reaction with dry $In(OTf)_3$ prepared by heating in vacuo before use. As expected, the yield of cyclic product **2aA** was reduced to only 5%, and the allylated adduct **3aA** was obtained as a major product (entry 5). Interestingly, we also found that the addition of 1 equiv of water to the reaction mixture restored the chemical yield to 88% (entry 6). In this case, the amount of $In(OTf)_3$ could be reduced to 10 mol % with no significant effects. We examined several proton sources as additives for the reactions with Ni, Pt, and Au catalysts. Among those examined, including AcOH, ArOH, CF_3CH_2OH, *t*-BuOH, and water, the highest yield of the desired product **2aA** was given by CF_3CH_2OH, which was obtained in good yield with Ni(II) and Au(I) catalysts (entries 7−10). In particular, a combined catalyst prepared from $AuCl(PPh_3)$ and $AgNTf_2$[14] showed remarkable catalytic activity, catalyzing the reaction efficiently at room temperature, while the other catalysts required heating at 70 °C. Furthermore, we investigated the additives for the In-(III)-catalyzed reaction. It was found that CF_3CH_2OH had only a marginal effect on the reactivity, but the addition of 2,6-di-*tert*-butyl-4-methoxyphenol (2 equiv) significantly accelerated the tandem cyclization, the reaction being complete within 6 h at 70 °C (entries 11 and 12). The unique roles of the phenol would be not only a proton source for the vinylindium intermediate but also an activator of the allylstannane reagent by forming an "-ate" complex.[15]

SCHEME 2. Plausible Reaction Mechanism of Lewis Acid-Catalyzed Tandem Addition and Cyclization Reaction



On the other hand, another aspect of the reactions with Ni, Pt, and Au catalysts is that the allylated product **3aA** was not obtained at all, whatever the reaction time, and this is totally different from the In(III)-catalyzed reaction. The same phenomenon was observed in Yamamoto's Ag(I)-catalyzed cyclization[5d] (path b in Scheme 1). Unlike $In(OTf)_3$, these soft Lewis acids do not promote the nucleophilic addition of allylstannane to the C═N double bond, and therefore, allylated product **3aA** was not obtained irrespective of the presence of the proton source. In this way, the soft transition-metal-catalyzed reactions seem to proceed via the iminium intermediate as shown in Scheme 2b. Although the vinylindium species **A** is proposed as an intermediate, direct protonation of the C≡C triple bond with water activated by $In(OTf)_3$ might be involved in the tandem addition and cyclization with the allylstananne reagent.

Tandem Addition and Cyclization of 2-(1-Alkynyl)arylaldimines with Various Nucleophiles. We examined the scope and limitations of the tandem reaction with several stannyl reagents using three effective catalysts, $In(OTf)_3$, $NiCl_2$, and $AuCl(PPh_3)/AgNTf_2$ (Table 2). Initial screening of the catalysts with methallyltributylstannane **4B** revealed that $In(OTf)_3$ was the best catalyst in terms of reaction rate and chemical yield

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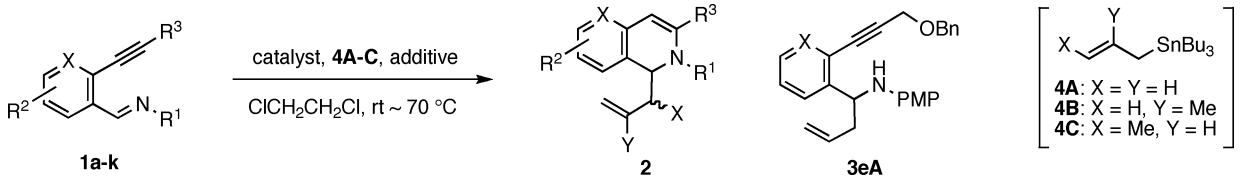
TABLE 2. Lewis Acid-Catalyzed Tandem Reaction of 1a−k with Allylic Stannanes 4A−C[a]



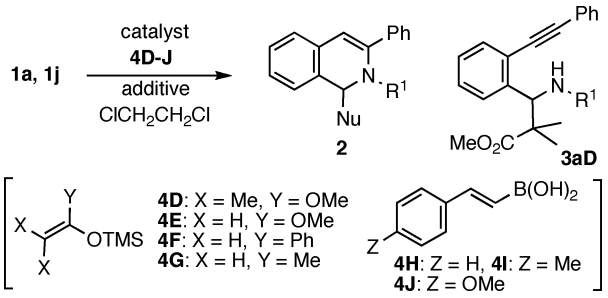
entry	1	R^1	R^2	R^3	X	method[b]	4	time (h)	2	yield[c] %
1	**1a**	RPMP	H	Ph	CH	**A**	**4B**	6	**2aB**	89
2	**1a**	PMP	H	Ph	CH	**B**	**4B**	48	**2aB**	70
3	**1a**	PMP	H	Ph	CH	**C**	**4B**	40	**2aB**	66
4	**1a**	PMP	H	Ph	CH	**A**	**4C**	6	**2aC**	80[d]
5	**1b**	PMP	H	4-MeOPh	CH	**A**	**4A**	8	**2bA**	71
6	**1c**	PMP	H	4-CF_3Ph	CH	**A**	**4A**	8	**2cA**	*e*
7	**1d**	PMP	H	*n*-Pr	CH	**A**	**4A**	8	**2dA**	89
8	**1e**	PMP	H	CH_2OBn	CH	**A**	**4A**	8	**2eA**	0[f]
9	**1f**	PMP	5-F	Ph	CH	**A**	**4A**	10	**2fA**	87
10	**1g**	PMP	5-OMe	Ph	CH	**A**	**4A**	12	**2gA**	70
11	**1h**	PMP	H	Ph	N	**A**	**4A**	8	**2hA**	72
12	**1i**	*i*-Bu	H	Ph	CH	**A**	**4A**	7	**2iA**	82
13	**1j**	Bn	H	Ph	CH	**A**	**4A**	9	**2jA**	70
14	**1k**	(*R*)-phenytyl	H	Ph	CH	**A**	**4A**	6	**2kA**	85[d]

[a] Reaction was carried out with **4A−C** (1.2−2.0 equiv), additive (2 equiv), and catalyst (0.2 equiv) in $ClCH_2CH_2Cl$. [b] **A**: $In(OTf)_3$, 2,6-di-*tert*-butyl-4-methoxyphenol, 70 °C; **B**: $NiCl_2$, CF_3CH_2OH, 70 °C; **C**: $AuCl(PPh_3)/AgNTf_2$, CF_3CH_2OH, room temperature. [c] Isolated yield. [d] Product was obtained as a mixture of two diastereomers in a ratio of 1:2. [e] Reaction gave a complex mixture. [f] Addition adduct **3eA** was only obtained in 60% yield.

(entries 1−3); thus, we selected it for further study. Sterically hindered crotylstannane **4C** also underwent the addition to imine **1a**, affording tandem adduct **2aC** in 80% yield with moderate diastereoselectivity (2:1) (entry 4). The reactions of various 2-(1-alkynyl)arylaldimine **1b−k** with allylstannane **4A** were carried out under the optimized reaction conditions. The R^3 substituent proved to have a significant influence on the cyclization. Although the reaction of **1b**, having a *p*-methoxyphenyl group as the R^3 substituent, afforded cyclic product **2bA** in good yield, the reaction of **1c**, with an electron-withdrawing group (*p*-CF_3-phenyl), resulted in a complex mixture of products (entries 5 and 6). We assumed that these contrasting results were attributable to a decrease of electronic density of the C≡C triple bond, which would be crucial for the coordination of the metal catalyst to the alkyne. In the case of **1d**, bearing an *n*-propyl group as the R^3 substituent, the corresponding adduct **2dA** was obtained in 89% yield. However, the benzyloxymethyl derivative **1e** did not undergo the tandem cyclization, giving only the addition product **3eA** in 60% yield (entries 7 and 8). On the other hand, concerning the R^2 substituent, introducing either electron-donating or -withdrawing groups to the substrate had no influence on the tandem reaction. Even replacement of the benzene ring by a pyridine ring was tolerated (entries 9−11). We have used the PMP-imines **1a−h** in the previous experiments (R^1 = PMP), but it was proven that both *i*-butyl and benzyl groups could be used as the nitrogen substituent (R^1) (entries 12 and 13). To develop the diastereoselective tandem reaction, the chiral imine **1k**, prepared from (*R*)-phenethylamine, was subjected to the same reaction conditions. The desired product **2kA** was obtained in 85% yield with moderate diastereoselectivity (2:1) (entry 14).

The tandem cyclization was explored with other nucleophiles such as ketene silyl acetals and alkenylboronic acids (Table 3). The In(III)-catalyzed reaction of ketene silyl acetal **4D** was carried out at 70 °C with PMP-imine **1a**, but only the additional adduct **3aD** was obtained (entry 1). In our attempt to make the R^1 substituent more nucleophilic, we found that the benzylimine derivative **1j** gave the desired product **2jD** selectively with 90%

TABLE 3. Lewis Acid-Catalyzed Tandem Reaction of 1a and 1j with Silyloxy Compounds 4D−G and Alkenylboronic Acids 4H−J[a]



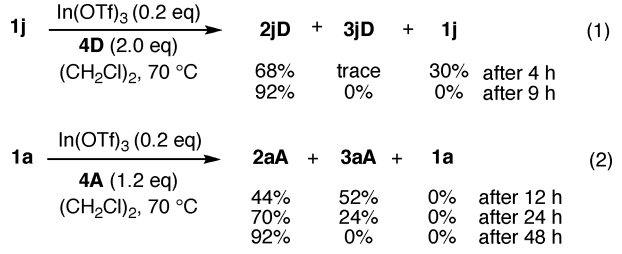
entry	1	method[b]	4D−H	time (h)	2	yield[c] (%)
1	**1a**	A	**4D**	8	**2aD**	0[d]
2	**1j**	A	**4D**	9	**2jD**	90
3	**1j**	A	**4E**	12	**2jE**	88
4	**1j**	A	**4F**	12	**2jF**	78
5	**1j**	A	**4G**	12	**2jG**	87
6	**1a**	B	**4H**	12	**2aH**	0[e]
7	**1a**	C	**4H**	5	**2aH**	75
8	**1a**	C	**4I**	5	**2aI**	80
9	**1a**	C	**4J**	5	**2aJ**	82

[a] Reaction was carried out with **4D−J** (2 equiv) and catalyst (0.2 equiv) in $ClCH_2CH_2Cl$. [b] **A**: $In(OTf)_3$, 70 °C; **B**: $In(OTf)_3$, H_2O (5 equiv), 70 °C; **C**: $AuCl(PPh_3)/AgNTf_2$, H_2O (5 equiv), room temperature. [c] Isolated yield. [d] Addition adduct **3aD** was obtained in 68% yield. [e] Only starting material **1a** was recovered.

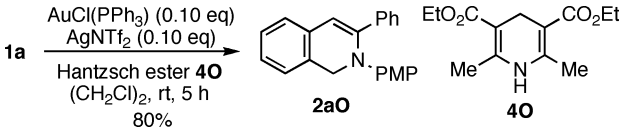
yield (entry 2). Further study on the reactions of **1j** with other siloxy compounds **4E−G** demonstrated that not only ketene silyl acetal derived from methyl acetate but also silyl enol ethers derived from acetone or acetopheneone could be used as nucleophiles to give the cyclic adducts **2jE−jG** in comparable yields (entries 3−5). Encouraged by these successful results using ketene silyl acetals, we were intrigued by Petasis-type[16] nucleophilic cyclization using alkenylboronic acids **4H−J**, by

(16) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

SCHEME 3. In(III)-Catalyzed Tandem Reaction of 1a and 1j with Allylstannane 4A and Ketene Silyl Acetal 4D



SCHEME 4. Synthesis of 1,2-Dihydroisoquinoline 2aO

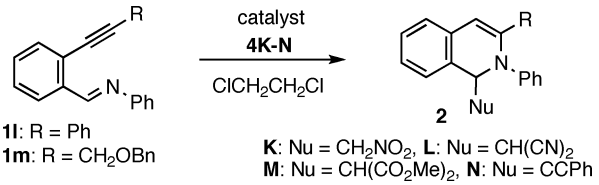


which several alkenyl groups can be introduced at the C_1 position of 1,2-dihydroisoquinolines. After many experiments, the best results were obtained using $AuCl(PPh_3)/AgNTf_2$ instead of $In(OTf)_3$, with the addition of water, and the reaction proceeded favorably at room temperature (entries 6 and 7). The alkenylboronic acids with more electron-donating groups on the benzene ring provided the corresponding products **2aH**−**2aJ** with slightly improved yields (entries 8 and 9).

The reaction mechanism of the Au(I)-catalyzed alkenylative cyclization would be the same as the Ni(II)- and Au(I)-catalyzed allylated cyclization shown in Scheme 2b. That is, the Au(I)-catalyzed formation of the iminium intermediate occurs initially, followed by nucleophilic addition of the alkenylboronic acids activated by water to give the cyclized adducts **2aH**−**2aJ**. The detailed mechanism of the Petasis reaction is not yet clear.

To clarify the different reaction processes, depending on the nucleophiles such as ketene silyl acetal **4D** and allylstannane **4A**, we monitored the distribution of the reaction products by taking their ^{1}H NMR spectra at appropriate intervals (Scheme 3). In the case of the reaction with benzylimine **1j** and **4D**, noncyclized addition adduct **3jD** was scarcely observed in the reaction mixture, regardless of the reaction time. Instead of **3jD**, the starting material **1j** was recovered, together with the desired tandem product **2jD** (eq 1). Indeed, **1j** and **2jD** were obtained in 30 and 68% yields, respectively, after 4 h, while only **2jD** was obtained, in 92% yield, after 9 h. In sharp contrast to this reaction, when PMP-imine **1a** was reacted with **4A**, it rapidly disappeared, and both the cyclized adduct **2aA** and the allylated adduct **3aA** were observed during the course of the reaction (eq 2). In a former case, the iminium intermediate should be formed predominantly before the direct addition of **4D** to the imine **1j** (tandem cyclization and nucleophilic addition mechanism) because the silylamide species of addition product **3aD** would not give cyclized product **2aD**, even in the presence of $In(OTf)_3$ (entries 1 and 2, Table 3). On the other hand, the latter reaction could be explained based on the mechanism shown in Scheme 2a (tandem nucleophilic addition and cyclization mechanism). The different outcomes between PMP-imine **1a** and benzylimine **1j** could be attributed to the nucleophilicity of the imine-nitrogen atoms to the C≡C triple bond activated by the In(III) catalyst. The more nucleophilic benzylimine **1j** tends to form the iminium intermediate more rapidly, resulting in the predominant production of cyclized adduct **2jD**. As described previously, tandem nucleophilic addition and cyclization reactions of 2-(1-alkynyl)aldimines **1a**−**k** with several organometallic reagents **4A**−**J** took place smoothly, using appropriate Lewis acids and proton sources, to give a wide range of 1,3-disubstituted 1,2-dihydroisoquinolines. The proton donors were shown to have roles not only in the regeneration of the catalyst but also in activation of the nucleophile.

TABLE 4. Lewis Acid-Catalyzed Tandem Reaction of 1a,e with Active Methylene Compounds 4K−N[a]



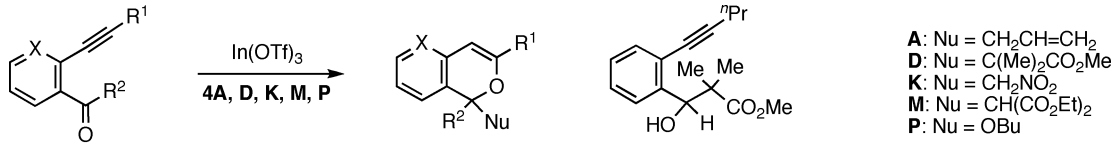
entry	1	nucleophile 4K−N	method[b]	time (h)	2	yield[c] (%)
1	**1l**	CH_3NO_2 **4K**	**A**	**12**	**2lK**	89
2	**1l**	CH_3NO_2 **4K**	**B**	**24**	**2lK**	86
3	**1l**	CH_3NO_2 **4K**	**C**	**7**	**2lK**	89
4	**1l**	$CH_2(CN)_2$ **4L**	**C**	**6**	**2lL**	75
5	**1l**	$CH_2(CO_2Me)_2$ **4M**	**C**	**6**	**2lM**	72
6	**1l**	PhCCH **4N**	**C**	**6**	**2lN**	91
7	**1m**	CH_3NO_2 **4K**	**B**	**24**	**2mK**	86
8	**1m**	CH_3NO_2 **4K**	**C**	**8**	**2mK**	83

[a] Reaction was carried out with **4K**−**N** (2.0 equiv) and catalyst (0.1−0.2 equiv) in $ClCH_2CH_2Cl$. [b] **A**: $In(OTf)_3$ (0.2 equiv), 70 °C; **B**: $NiCl_2$ (0.1 equiv), 70 °C; **C**: $AuCl(PPh_3)/AgNTf_2$ (0.1 equiv), room temperature. [c] Isolated yield.

We tried the same reaction with active methylene compounds as the nucleophile (Table 4), which would be a more benign process from the viewpoint of atom efficiency. We first employed activated nitromethane **4K** as a nucleophile for the tandem reaction. For this purpose, three catalytic systems were examined. The intended tandem reaction proceeded with all catalysts, $AuCl(PPh_3)/AgNTf_2$ being the most effective in terms of reaction temperature and reaction rate (entries 1−3). Although a similar Ag(I)-catalyzed tandem reaction with active methylene compounds has been reported by Yamamoto's group, our reaction conditions were much milder as compared with theirs, which required heating at 80 °C.[5d] For the tandem reaction, more functionalized nucleophiles such as malononitrile **4L** and dimethyl malonate **4M** could be used in the presence of a $AuCl(PPh_3)/AgNTf_2$ catalyst to provide the corresponding tandem products **2lL** and **2lM** in good yields (entries 4 and 5). In addition, the terminal alkyne **4N** proved to be an effective nucleophile for this tandem reaction (entry 6). These studies prompted us to examine the scope and limitations of substrate for this tandem reaction. The In(III)-catalyzed cyclization of **1e**, bearing a benzyloxymethyl group as the substituent (R), did not afford the desired product (Table 2, entry 8). However, we found that both catalysts, $NiCl_2$ and $AuCl(PPh_3)/AgNTf_2$, are effective enough to promote the tandem cyclization of **1m** with nitromethane, giving the product **2mK** in high yields. We assumed that both catalysts would activate the C≡C triple bond efficiently without inhibition of the imine and ether moieties due to their more carbophilic character than $In(OTf)_3$.

Having established the optimal conditions for the reactions with carbon nucleophiles, the tandem cyclization accompanied by hydride reduction of the iminium intermediate was next investigated using various reducing agents. Although use of Et_3SiH was not effective for this purpose, the desired cyclic adduct **2aO** was obtained in 80% yield by the reaction of **1a** with 2

TABLE 5. In(III)-Catalyzed Tandem Reaction of Aldehydes 5a−d with Various Nucleophiles 4[a]



5a-d **6** **7aD**

entry	5	R^1	R^2	X	nucleophile **4**	method[b]	time (h)	6	yield[c] (%)
1	**5a**	*n*-Pr	H	CH	**4A**	**A**	21	**6aA**	75
2	**5a**	*n*-Pr	H	CH	**4D**	**B**	15	**6aD**	0[d]
3	**5a**	*n*-Pr	H	CH	**4K**	**B**	48	**6aK**	0[e]
4	**5a**	*n*-Pr	H	CH	**4M**	**B**	48	**6aM**	35[f]
5	**5a**	*n*-Pr	H	CH	*n*-BuOH **4P**	**C**	18	**6aP**	92
6	**5b**	Ph	H	CH	**4A**	**A**	21	**6bA**	85
7	**5c**	Ph	H	CH	**4A**	**A**	21	**6cA**	85
8	**5d**	Ph	Me	CH	**4A**	**A**	21	**6dA**	80

[a] Reaction was carried out with **4** (1.2−6.0 equiv) and $In(OTf)_3$ (0.2 equiv). [b] **A**: **4A** (1.2 equiv), $ClCH_2CH_2Cl$, room temperature; **B**: **4D**, **4K**, **4M** (2 equiv), 1,4-dioxane, room temperature; **C**: *n*-BuOH (6 equiv), DMF, 50 °C. [c] Isolated yield. [d] Addition adduct **7aD** was obtained in 72% yield. [e] Only starting material **5a** was recovered. [f] Starting material **5a** was recovered in 30% yield.

equiv of Hantzsch ester **4O**[17] in the presence of $AuCl(PPh_3)/AgNTf_2$ catalyst (0.1 equiv) (Scheme 4).[18]

Tandem Addition and Cyclization of 2-(1-Alkynyl)arylaldehydes. The new catalysts such as $In(OTf)_3$, $NiCl_2$, and $AuCl(PPh_3)/AgNTf_2$ expanded the applicability of the tandem nucleophilic addition and cyclization with 2-(1-alkynyl)arylaldimine. Therefore, we turned our attention to the tandem reaction of 2-(1-alkynyl)arylaldehydes with the aim of concise synthesis of 1*H*-isochromenes (Table 5). Although such a transition-metal-catalyzed transformation of 2-(1-alkynyl)arylaldehydes **5** into 1*H*-isochromenes has been accomplished in the presence of a proton source with Pd(0) and Cu(II) catalysts,[19] Au(III)- and Cu(II)-catalyzed reactions of **5** in the presence of external alkynes or alkenes afforded polycyclic compounds via [4 + 2]benzannulation.[20] Therefore, we examined the $In(OTf)_3$-catalyzed tandem reactions of **5a**−**d** with various nucleophiles in the absence of proton sources. In fact, the reaction with silyl enol ether **4D** provided no cyclic adduct **6aD**, but the desired product **6aA** was obtained as the single product in the reaction with allylstannane **4A** (entries 1 and 2). In contrast to nitromethane **4K**, dimethyl malonate **4M** could be introduced to **5a** in dioxane, furnishing the corresponding cyclic compound **6aM** in moderate yield (entries 3 and 4). Treatment of aldehyde **5a** with *n*-BuOH in DMF at 50 °C afforded the tandem cyclic product **6aP** in 92% yield but not the expected dibutyl acetal (entry 5). The reaction with allylstannane **4A** has the advantages of lower catalyst quantity and higher product yield, as compared with reported methods.[19g] We examined the In(III)-catalyzed tandem allylated cyclization with some 2-(1-alkynyl)arylaldehydes **5b**,**c**. All tandem reactions proceeded efficiently irrespective of the R^1 substituent and the ring system (entries 6 and 7). Furthermore, ketone derivative **5d** also underwent tandem cyclization to give the corresponding adduct **6dA**, without any contamination by the addition product **7dA** (entry 8). To elucidate the mechanism, the reaction mixture of **5a**, $In(OTf)_3$,

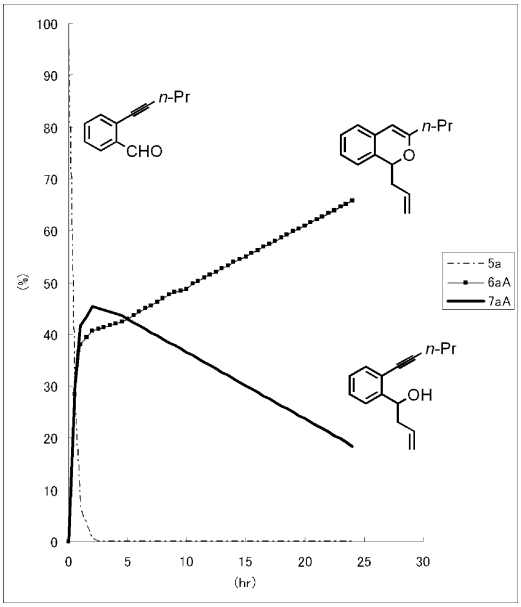


FIGURE 1. Time-dependent product distribution of **6aA** and **7aA** in the reaction of aldehyde **5a** with allylstannane **4A**.

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and allylstannane **4A** was monitored by ^{1}H NMR (Figure 1). Almost all the starting material disappeared after 2 h, and both allylated product **7aA** and cyclic product **6aA** were observed in the reaction mixture. The amount of **7aA** gradually decreased with increasing yield of **6aA**. From these results, the tandem addition and cyclization of 2-(1-alkynyl)arylaldehydes **5a**−**c** with allyltributylstannane **4A** seems to take place in the same manner as that of 2-(1-alkynyl)arylimines **1**.

Conclusion

In conclusion, concise synthesis of 1,3-disubstituted 1,2-dihydroisoquinolines was established by tandem nucleophilic addition and cyclization of 2-(1-alkynyl)arylaldimines and various nucleophiles in the presence of carbophilic Lewis acids such as $In(OTf)_3$, $NiCl_2$, and $AuCl(PPh_3)/AgNTf_2$. Among these catalysts, Ni(II) and Au(I) catalysts require appropriate proton sources to proceed the tandem reaction, by which a wide range of nucleophiles and substrates can be employed for these reactions. We have demonstrated that these reactions proceeded via two different reaction pathways depending on the character of catalyst and the reactivity of substrate and nucleophile: one is the initial addition of nucleophile to the C═N double bond and the subsequent cyclization of the resulting amide species to the C≡C triple bond, and the second one is the nucleophilic addition of imine to the C≡C triple bond activated by the catalyst and the subsequent addition of nucleophile to the resultant iminium species. Furthermore, the In(III)-catalyzed tandem reaction can be applied to 2-(1-alkynyl)arylaldehydes for the efficient synthesis of 1*H*-isochromenes.

Experimental Section

General Procedure for the In(III)-Catalyzed Tandem Reaction of Imines with Allyltributylstannane as a Nucleophile. To a solution of imine (0.20 mmol) in CH_2ClCH_2Cl (0.40 mL) were added 2,6-di-*tert*-butyl-4-methoxyphenol (0.40 mmol), allyltributylstannane (0.24 mmol), and $In(OTf)_3$ (0.040 mmol), and the mixture was stirred at 70 °C for 6−12 h. After the reaction was complete, the reaction mixture was diluted with H_2O (3 mL) and extracted with $CHCl_3$ (3 × 2 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/AcOEt = 5:1) to give product.

1-Allyl-1,2-dihydro-2-(4-methoxyphenyl)-3-phenylisoquionline (2aA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 6.7 Hz, 2H), 7.25−7.21 (m, 6H), 7.13 (t, J = 5.4 Hz, 1H), 6.97 (d, J = 6.3 Hz, 1H), 6.84 (d, J = 7.0 Hz, 2H), 6.62 (d, J = 6.3 Hz, 2H), 6.57 (s, 1H), 6.15−6.11 (m, 1H), 5.23−5.17 (m, 2H), 4.83 (dd, J = 5.1, 4.9 Hz, 1H), 3.65 (s, 3H), 2.75−2.72 (m, 1H), 2.30−2.25 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 141.3, 140.9, 137.9, 135.8, 132.3, 131.8, 128.2, 127.7, 127.2, 126.1, 125.6, 124.2, 124.0, 117.8, 113.9, 110.7, 66.3, 55.3, 39.5; IR ($CHCl_3$) 3643, 2960, 2360, 1508 cm^{-1}; LRMS (FAB) *m*/*z* 354 (MH^+); HRMS (FAB) calcd for $C_{25}H_{24}NO$ (MH^+) 354.1858, found 354.1866.

General Procedure for the Au(I)-Catalyzed Tandem Reaction of Imines with Alkenylboronic Acids as a Nucleophile. To a solution of $AuCl(PPh_3)$ (0.016 mmol) and $AgNTf_2$ (0.016 mmol) in dioxane (0.40 mL) were added imine (0.016 mmol), alkenylboronic acid (0.32 mmol), and 6.0 μL of water, and the resulting mixture was stirred at room temperature for 5 h. After the reaction was complete, the reaction mixture was diluted with H_2O (3 mL) and extracted with $CHCl_3$ (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/AcOEt = 5:1) to give product.

1,2-Dihydro-2-(4-methoxyphenyl)-3-phenyl-1-styrylisoquinoline (2aH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.7 Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.26−7.17 (m, 6H), 7.09−7.07 (m, 1H), 6.90 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 6.60−6.57 (m, 1H), 6.52−6.47 (m, 1H), 6.43 (s, 1H), 5.51 (d, J = 5.2 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 141.3, 141.2, 137.8, 136.9, 132.3, 130.6, 130.1, 129.0, 128.5, 128.0, 127.8, 127.5, 126.7, 126.3, 126.0, 124.1, 123.94, 113.9, 109.8, 67.2, 55.4; IR ($CHCl_3$) 3027, 2966, 2366, 1731, 1260 cm^{-1}; LRMS (EI) *m*/*z* 415 (M^+); HRMS (EI) calcd for $C_{19}H_{24}O_5$ (M^+) 415.1936, found 415.1935.

General Procedure for the In(III)-Catalyzed Tandem Reaction of Aldehydes with Allyltributylstannane as a Nucleophile. To a solution of aldehyde (1.0 mmol) in CH_2ClCH_2Cl (2 mL) were added allyltributylstannane (1.2 mmol) and $In(OTf)_3$ (0.20 mmol), and the resultant mixture was stirred at room temperature for 21 h. After the reaction was complete, the reaction mixture was diluted with H_2O (3 mL) and extracted with $CHCl_3$ (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 5:1) to give product.

1-Allyl-3-propyl-1*H*-isochromene (6aA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18−7.15 (m, 1H), 7.10−7.07 (m, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.92 (d, J = 7.3 Hz, 1H), 5.93−5.85 (m, 1H), 5.58 (s, 1H), 5.16−5.11 (m, 2H), 5.09 (s, 1H), 2.77−2.71 (m, 1H), 2.47−2.43 (m, 1H), 2.18−2.11 (m, 2H), 1.64−1.58 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.3, 127.8, 125.5, 124.1, 122.8, 117.5, 100.1, 98.3, 80.2, 77.4, 38.7, 35.9, 20.0, 13.7, 13.5; IR ($CHCl_3$) 3028, 2964, 2933, 2875, 1725 cm^{-1}; LRMS (FAB) *m*/*z* 215 (MH^+); HRMS (FAB) calcd for $C_{15}H_{19}O$ (MH^+) 215.1436, found 215.1431.

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Supporting Information Available: Product characterization data for 1,2-dihydroisoquinolines and ^{1}H NMR spectra for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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