論文の内容の要旨

論文題目　Catalytic Asymmetric Alkynylation of Carbonyl Compounds by an Indium(III) Catalyst via Dual Activation of Soft Pro-Nucleophiles and Hard Electrophiles
（インジウム(III)触媒による末端アルキンのカルボニル化合物への不斉付加反応の研究）

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The addition of terminal alkynes to aldehydes and ketones, especially in an enantioselective manner, is of great interest because of the versatility of the corresponding propargylic alcohols. Stoichiometric amounts of strong bases such as organolithium or dialkylzinc reagents are widely used for this type of reaction with or without chiral ligands or chiral Lewis acid complexes. Intrinsic drawbacks, however, such as the use of stoichiometric amounts of metal reagents and a separate metal acetylide preparation step, make it difficult to achieve an atom-economical process.

Given the recent strong demand for an environmentally-benign process with high total efficiency, the in situ catalytic generation of metal nucleophiles and their use in carbon–carbon bond-forming reactions is currently a major interest in organic synthesis. The use of only catalytic amounts of chiral metal salts to achieve *truly catalytic* asymmetric reactions using terminal alkynes directly as a substrate is eagerly anticipated. Carreira and coworkers reported the sophisticated example of a catalytic system of $Zn(OTf)_2$, *N*-methylephedrine, and Et_3N.[1] Due to the Cannizzaro reaction, however, aromatic aldehydes cannot be used in this catalytic system. Another catalytic alkynylation of aldehydes and ketones using a catalytic amount of strong hydroxide, alkoxide, or phosphazene base in polar solvents has also been reported, although the substrate generality is still limited and there has been no application to the catalytic enantioselective reactions using these bases. Thus, there remains much room to develop catalytic alkynylation of various carbonyl compounds under mild conditions.

1. Development of a New catalytic System for the Alkynylation of Aldehydes and Ketones[2]

Shibasaki's group has developed various bifunctional catalysts, such as heterobimetallic catalysts and Lewis acid–Lewis base catalysts, to achieve efficient enantioselective reactions under mild conditions with minimal undesired waste. Application of this bifunctional strategy seems to be one of the most promising solutions for developing a catalytic alkynylation of a broad range of aldehydes and ketones. From this point of view, dual activation of soft pro-nucleophiles (terminal alkynes) and hard electrophiles (carbonyl compounds) is very important. Indium(III) salts are efficient Lewis acids for carbonyl compounds. Quite recently, indium(III) salts have emerged as effective activators of alkynyl groups in cross-coupling reactions, etc. This "bifunctional character" of indium(III) prompted me to examine indium(III) salts for the alkynylation of carbonyl compounds via dual activation (Scheme 1).

Scheme 1. Alkynylation via Dual Activation of Both Carbonyl Compounds and Alkynes

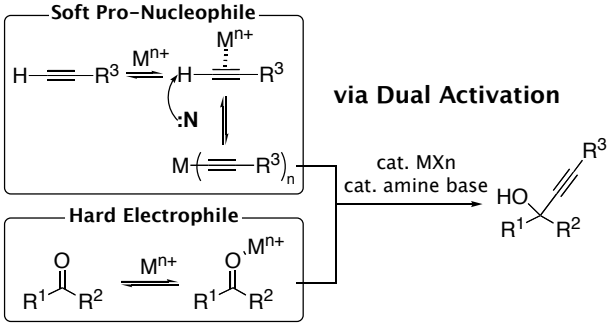
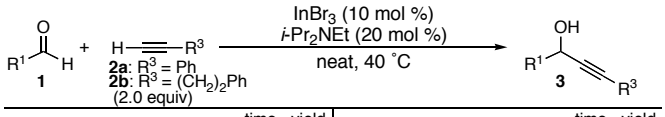


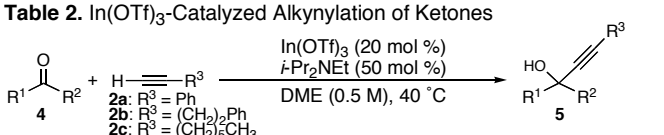
Table 1. $InBr_3$-Catalyzed Alkynylation of Aldehydes



entry	aldehyde	alkyne	time (h)	yield (%)	entry	aldehyde	alkyne	time (h)	yield (%)
1[a]	**1a**	**2a**	10	84	7	**1g**	**2a**	5	93
2	**1b**	**2a**	44	73	8	**1h**	**2a**	10	98
3	**1c**	**2a**	48	88	9		**2b**	42	75
4	**1d**	**2a**	44	63	10	**1i**	**2a**	10	99
5[a]	**1e**	**2a**	24	86	11	**1j**	**2a**	24	82
6	**1f**	**2a**	22	73	12	**1k**	**2a**	48	62

[a] DME was used as a solvent (5.0 M).

Table 2. $In(OTf)_3$-Catalyzed Alkynylation of Ketones



entry	ketone	alkyne	time (h)	yield (%)	entry	ketone	alkyne	time (h)	yield (%)
1	**4a**: R = H	**2a**	24	90	7	**4d**	**2a**	10	85[f]
2[a]		**2a**	63	92					
3[b]		**2b**	48	85	8[b]	**4e**	**2a**	48	58[g]
4[b]		**2c**	48	74	9[b,c]	**4f**	**2a**	48	61
5	**4b**: R = Me	**2a**	24	90[d]					
6	**4c**: R = *t*-Bu	**2a**	60	94[e]	10[b,c]	**4g**	**2a**	48	64

[a] Performed with 10 mol % $In(OTf)_3$. [b] Concentration was 5.0 M. [c] Performed with 5.0 equiv of alkyne. [d] dr =1.3:1. [e] dr =2:1. [f] dr =1.1:1. [g] dr =5.2:1.

Using cyclohexanecarboxaldehyde (**1a**) or benzaldehyde (**1b**) with phenylacetylene (**2a**) as representative substrates, I started to examine alkynylation of aldehydes using indium(III) salts under various conditions and found that the combination of $InBr_3$ with *i*-Pr_2NEt provided the optimal reaction efficiency in the alkynylation of aldehydes. As summarized in Table 1, the optimized reaction conditions were applicable for a wide range of aldehydes.

The use of ketones instead of aldehydes, however, gave the corresponding tertiary propargylic alcohols in very low yield under these conditions. For ketones, $In(OTf)_3$ (20 mol %) was found to be the indium source of choice and the results are shown in Table 2. Just changing the indium source, these catalytic systems provided the broad substrate scope, including ketones, under mild conditions.[2]

Dual activation of both soft pro-nucleophiles and hard electrophiles is the key to this reaction and was confirmed in the mechanistic studies using in situ IR and NMR spectroscopic analysis. First, to gain information about the activation of alkyne, in situ IR spectra were measured. When 1 equiv of phenylacetylene was added to the solution of $InBr_3$ and *i*-Pr_2NEt, there was a signal at 3246 cm^{-1} corresponding to the C–H stretch of the alkyne, and this signal disappeared in less than 1 min. On the other hand, when 1 to 3 equiv of **2a** was added (total 2 to 4 equiv),

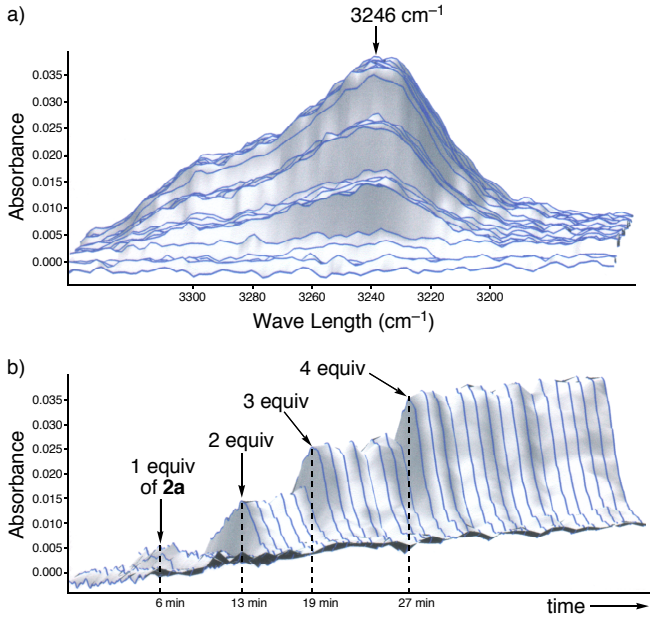


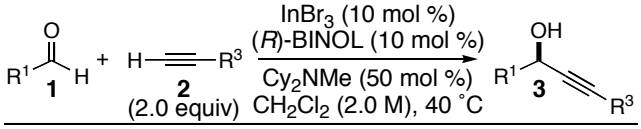
Figure 1. In situ IR study of the successive addition of phenylacetylene (**2a**) to $InBr_3$ and *i*-Pr_2NEt in DME. a) the C-H stretch signal of **2a**, b) time course of the successive addition (1-4 equiv of phenylacetylene) at 3246 cm^{-1}.

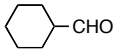
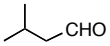
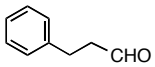
the absorbance at 3246 cm^{-1} increased with each addition. These results suggested that $InBr_3$ activated the terminal alkyne and that the indium monoacetylide species was formed. Next, to confirm the activation of the carbonyl compound by Lewis acidic indium(III) salt, NMR spectroscopic analysis was performed using $InBr_3$. The shift of the peak corresponding to the aldehyde proton (in ^1H NMR spectrum) and carbonyl carbon (in ^{13}C NMR spectrum) was observed following the addition of $InBr_3$ to aldehyde in the presence or absence of *i*-Pr_2NEt and phenylacetylene (**2a**), indicating the activation of the carbonyl compound by coordination to the indium(III) species.

2. Development of Catalytic Asymmetric Alkynylation of Aldehydes[3]

The success in developing mild reaction conditions prompted me to further develop asymmetric variants to produce versatile optically-active propargylic alcohols. Initial studies on the development of the asymmetric reaction conditions revealed that the use of BINOL as a chiral ligand had high enantioselectivity in the addition of phenylacetylene (**2a**) to cyclohexanecarboxaldehyde (**1a**); in the presence of 10 mol % $InBr_3$, 10 mol % (*R*)-BINOL (1:1 ratio), and 50 mol % *i*-Pr_2NEt in CH_2Cl_2 at 40 °C, the propargylic alcohol **3aa** was obtained in 96% ee, although the chemical yield was moderate (46%, after 7 h). Further optimization of reaction conditions led to the finding that the use of Cy_2NMe instead of *i*-Pr_2NEt effectively accelerated the reaction, giving the product in 84% yield and 98% ee (after 7 h).

Table 3. $InBr_3$/BINOL Complex-Catalyzed Asymmetric Alkynylation of Aliphatic Aldehydes

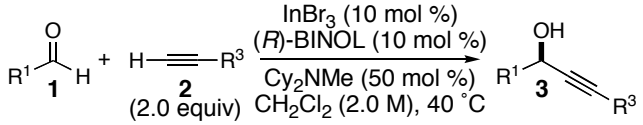


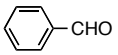
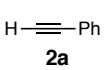
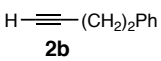
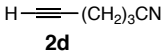
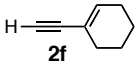
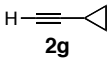
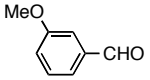
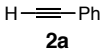
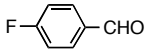
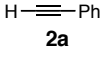
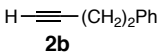
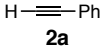
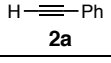
entry	aldehyde	alkyne	time (h)	yield (%)	ee (%)
1	 **1a**	H—≡—Ph **2a**	9	95	98
2		H—≡—$(CH_2)_2$Ph **2b**	36	77	>99
3		H—≡—$(CH_2)_3$CN **2d**	42	93	99
4		H—≡—$(CH_2)_3$Cl **2e**	42	91	85
5	 **1l**	H—≡—Ph **2a**	25	85	96
6		H—≡—$(CH_2)_2$Ph **2b**	48	46	98
7[a]	 **1m**	H—≡—Ph **2a**	24	85	98

[a] Aldehyde **1m** was slowly added over 22 h.

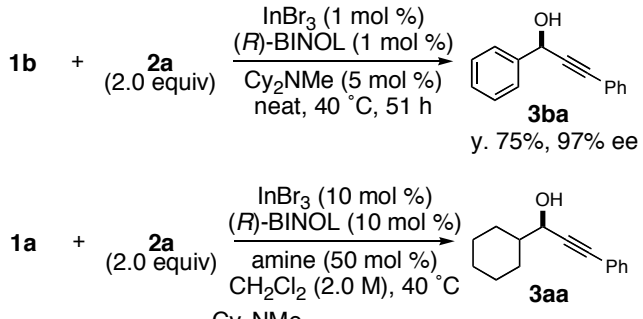
The generality of this catalytic system (10 mol % $InBr_3$ and (*R*)-BINOL, and 50 mol % Cy_2NMe in CH_2Cl_2 at 40 °C) was examined using aliphatic aldehydes, as summarized in Table 3. Even using the less reactive alkylacetylene **2b**, **2d**, and **2e** instead of phenylacetylene (**2a**), good chemical yield was obtained with excellent enantioselectivity (entries 2-4). Although aldehydes with a primary alkyl group could not be utilized in racemic system, the reaction with isovaleraldehyde (**1l**) also proceeded under the

Table 4. $InBr_3$/BINOL Complex-Catalyzed Asymmetric Alkynylation of Aromatic Aldehydes



entry	aldehyde		alkyne	time (h)	yield (%)	ee (%)
1		**1b**	 **2a**	24	84	95
2			 **2b**	48	70	98
3			 **2d**	48	68	98
4			 **2f**	48	77	89
5			 **2g**	48	74	83
6		**1d**	 **2a**	48	77	97
7		**1f**	 **2a**	24	75	95
8			 **2b**	45	61	99
9		**1k**	 **2a**	29	80	97
10		**1n**	 **2a**	20	84	98

Scheme 2. The Reaction Performed with 1 mol % of Catalyst under Neat Conditions



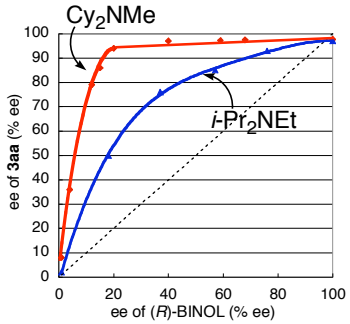


Figure 2. (+)-Nonlinear Effects in Asymmetric Alkynylation Catalyzed by $InBr_3$/BINOL Complex

same conditions in highly enantioselective manner (entries 5,6). Even for the very easily enolizable aldhehyde, hydrocinnamaldehyde (**1m**), slow addition of the aldehyde prevented side reactions such as self-condensation, providing the desired product in good yield and excellent enantioselectivity (entry 7).

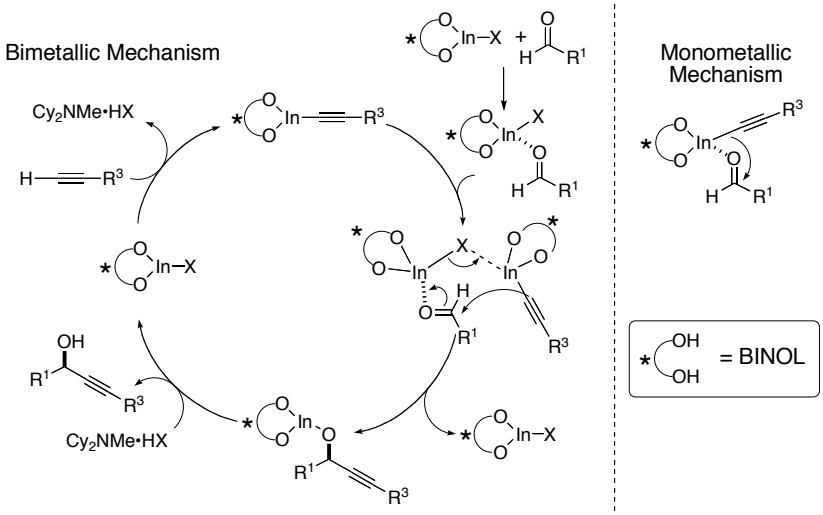
Furthermore, the optimized conditions were also applicable for aromatic aldehydes, which are quite challenging substrates for existing catalytic systems due to a competitive Cannizzaro reaction (Table 4). The addition of phenylacetylene (**2a**) to benzaldehyde (**1b**) proceeded smoothly to give the corresponding product **3ba** in 84% yield and 95% ee after 24 h. The use of the alkyl- and alkenylacetylenes also produced high enantioselectivity (entries 2-5). Especially, the accommodation of alkylalkynes having some functional group, such as **2d**, is noteworthy. In addition, benzaldehyde derivatives with the electron-donating substituent or electron-withdrawing substituent gave satisfactory yields and high enantioselectivity (entries 6-8). Heteroaromatic aldehydes, such as 3-thiophenecarboxaldehyde (**1k**) or 3-furaldehyde (**1n**) can also be utilized as electrophiles (entries 9,10).

Lowering the catalyst loading was possible; the use of 1-2 mol % of catalyst promoted the reaction of benzaldehyde (1b) with 2a, affording good yield and enantioselectivity, while longer reaction time was necessary. Notably, the reaction also proceeded under near conditions in highly enantioselective manner with 1 mol % of catalyst (Scheme 2).

To gain insight into the reaction mechanism, when the reaction was performed using nonenantiopure BINOL, rather strong positive nonlinear effects were observed between the enantiomeric excess of BINOL and the product (Figure 2). Several experiments revealed that the origin of nonlinear effects is a selective resolution process. The heterochiral complex derived from $InBr_3$, BINOL, and Cy_2NMe selectively caused a precipitaion. Thus, large amplification was

observed in the reaction; for example, the use of 20% ee of BINOL afforded the propargylic alcohol **3aa** in 94% ee. These experiments also implied the reactivity difference by the structure of amine base; the differenc of amine base would affect on the property or stability of catalyst complex.

Scheme 2-9. Proposed Catalytic Cycle



Although the precise mechanism is not clear at present, based on the dual activation mechanism that was confirmed in racemic system, proposed catalytic cycle is illustrated in Scheme 3; first, indium acetylide species would be generated via the activation of alkyne by indium complex. It could react with aldehyde that would also be activated by indium/BINOL complex. The resulting indium alkoxide should be protonated, leading to the regeneration of catalyst with releasing the propargylic alcohol. In the addition step, the monometallic mechanism cannot be completely excluded. The bimetallic mechanism, however, would be much more plausible by the following reasons; (1) The results obtained from NLE experiments (cf. Figure 2) as well as related experiments suggested the involvement of the bimetallic mechanism. (2) The reactivity is highly dependent on the ligand structure. (3) Intramolecular addition mechanism in the monometallic mechanism seems to be difficult. More precise mechanistic studies, including X-ray crystarographic analysis of catalyst, are ongoing.

I developed a new catalytic alkynylation of aldehydes and ketones by focusing on “bifunctional character” of indium(III). Dual activation of both soft nucleophiles and hard electrophiles is the key to this reaction and was confirmed by in situ IR and NMR spectroscopic studies. The asymmetric variant of this reaction was promoted by the In(III)/BINOL complex, giving the propargylic alcohols in highly enantioselective manner (83->99% ee). The striking feature is that this catalyst system is very simple, mild, and applicable for a wide range of substrates. It provides a new entry in bifunctional catalysis.

References:

(1) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.
(2) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363.
(3) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760.