

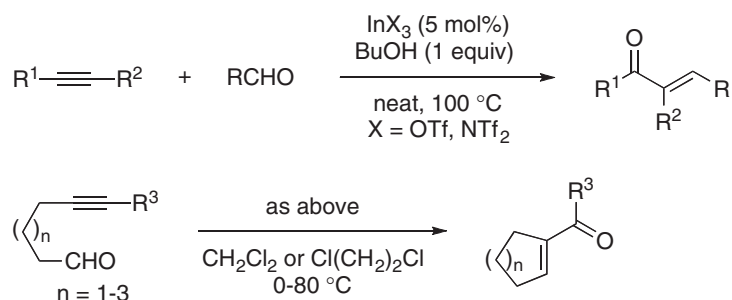
Indium(III)-catalyzed Coupling between Alkynes and Aldehydes to α,β -Unsaturated Ketones

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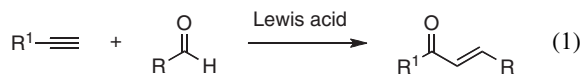
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Indium(III)-catalyzed Coupling between Alkynes and Aldehydes to α,β -Unsaturated KetonesKatsukiyo Miura,*¹ Kiyomi Yamamoto,² Aya Yamanobe,² Keisuke Ito,² Hidenori Kinoshita,¹ Junji Ichikawa,² and Akira Hosomi²¹Department of Applied Chemistry, Graduate School of Science and Engineering, Saitama University, Sakura-ku, Saitama 338-8570²Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571

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The combined use of a catalytic amount of InX_3 ($X = \text{OTf}$ and NTf_2) and 1-butanol was found to be effective in formal alkyne–aldehyde metathesis. With this catalytic system, aromatic alkynes reacted with aromatic aldehydes to give chalcones in moderate to good yields. Alkynals were efficiently converted into 5- to 7-membered cyclic compounds by intramolecular alkyne–aldehyde coupling.

The Lewis acid-promoted coupling between alkynes and aldehydes is known to form conjugated enones by cleavage of the aldehyde $\text{C}=\text{O}$ bond and formation of new $\text{C}=\text{C}$ and $\text{C}=\text{O}$ bonds (eq 1).^{1–3} The conventional methods for this formal alkyne–aldehyde metathesis require stoichiometric Lewis acids.^{1,2} Recent interest has been focused on catalytic alkyne–aldehyde metathesis.³ Several Lewis and Brønsted acids and transition-metal compounds have been reported to act as the catalyst, however there is much room to develop a new, efficient catalytic system. We herein report that the combined use of a catalytic amount of InX_3 ($X = \text{OTf}$ and NTf_2) and 1-butanol (BuOH) is effective in inter- and intramolecular coupling between alkynes and aldehydes.^{4,5}



We initially found that the $\text{In}(\text{OTf})_3$ -catalyzed reaction of phenylacetylene (**1a**) with benzaldehyde (**2a**) without solvent gave chalcone (**3aa**) in 35% yield. We then examined the effect of additives on this coupling. When one equivalent of BuOH was used, **3aa** was obtained in 73% yield (Entry 1 in Table 1).⁶ An increased amount of **1a** improved the yield.

The coupling with other aromatic aldehydes **2b** and **2c** gave the corresponding enones **3** in moderate yields (Entries 2 and 3), while the reaction with aliphatic aldehydes, *c*-HexCHO and $\text{Ph}(\text{CH}_2)_2\text{CHO}$, resulted in a complex mixture of products under the same conditions. Arylalkynes **1b–1d**, bearing an electron-donating group on the benzene ring, were as reactive as **1a** (Entries 4–6). In contrast, arylalkyne **1e**, bearing an electron-withdrawing group, was much less reactive than **1b–1d** (Entry 7). Similarly 1-dodecyne was quite insensitive to **2a**. Thus electron-rich, nucleophilic alkynes showed high reactivity toward the alkyne–aldehyde coupling. 1-Phenyl-1-propyne (**1f**) was more reactive than **1a**. The coupling of **1f** with aromatic and aliphatic aldehydes proceeded efficiently under catalysis by $\text{In}(\text{OTf})_3$ (Entries 8 and 9).⁷

To clarify the role of $\text{In}(\text{OTf})_3$, we examined the effect of $\text{In}(\text{OTf})_3$ on the ¹³C chemical shifts of **1a** and **2a** (Table 2). Adding $\text{In}(\text{OTf})_3$ to a 1:1 solution of **1a** and **2a** in CDCl_3 hardly affected the chemical shifts of the sp-carbons C(1) and C(2). In contrast, it brought about a downfield shift of the carbonyl

Table 1. In(III)-catalyzed alkyne–aldehyde coupling^a

$\text{R}^1\text{—}\text{C}\equiv\text{C—R}^2$ (1) + $\text{R}^3\text{—}\text{C}(=\text{O})\text{—H}$ (2)		$\xrightarrow[\text{0.5–2 h}]{\text{In}(\text{OTf})_3 (5 \text{ mol}\%), \text{BuOH} (1 \text{ equiv})}$		$\text{R}^1\text{—}\text{C}(=\text{O})\text{—C}(\text{R}^2)=\text{C}(\text{R}^3)\text{—R}^4$ (3)
Entry	R ¹	R ²	R	Yield/% ^{b,c}
1	Ph	H (1a)	Ph (2a)	73, 88 ^d
2	Ph	H	4-MeOC ₆ H ₄ (2b)	52, 58 ^d
3	Ph	H	4-BrC ₆ H ₄ (2c)	58 ^d
4	4-MeOC ₆ H ₄	H (1b)	Ph	78
5	4-MeC ₆ H ₄	H (1c)	Ph	61
6	2-MeC ₆ H ₄	H (1d)	Ph	73
7	4-CF ₃ C ₆ H ₄	H (1e)	Ph	4
8	Ph	Me (1f)	Ph	98
9	Ph	Me	<i>c</i> -Hex (2d)	88

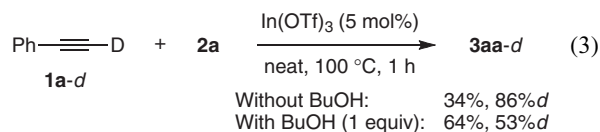
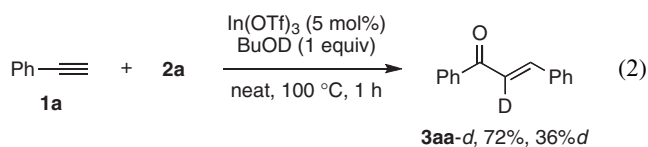
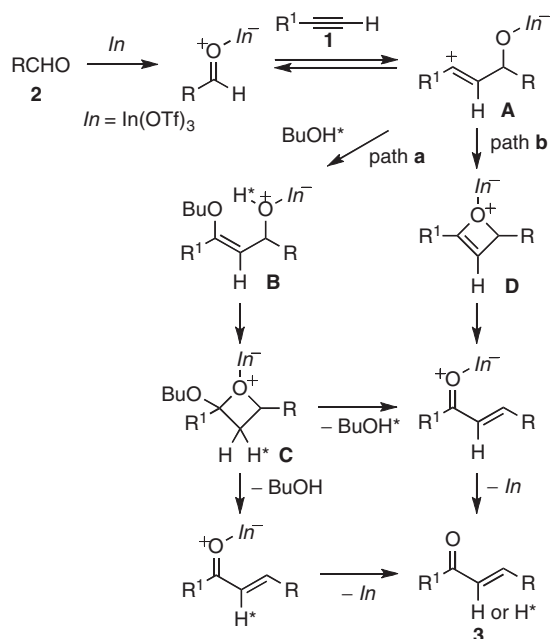
^aConditions: **1** (1.00 mmol), **2** (1.00 mmol), $\text{In}(\text{OTf})_3$ (0.05 mmol).^bIsolated yield. ^c*E*:*Z* = >98:2 (Entries 1–7). *E*:*Z* = 96:4 (Entry 8). *E*:*Z* = 92:8 (Entry 9). ^dWith 1.50 mmol of **1**.**Table 2.** ¹³C NMR Data for **1a** and **2a** in CDCl_3 at 25 °C^a

Position	¹³ C Chemical shifts (ppm)		
	No additive	$\text{In}(\text{OTf})_3$ ^{b,c}	$\text{In}(\text{OTf})_3$ ^{b,d} + BuOH ^e
C(1)	83.61	83.64	83.62
C(2)	77.16	77.12	77.10
C(3)	192.27	192.63	193.01

^aA solution of **1a** (0.05 mmol) and **2a** (0.05 mmol) in CDCl_3 (0.5 mL) was used for 67.7 MHz ¹³C NMR analysis. ^b $\text{In}(\text{OTf})_3$ (0.05 mmol). ^cPartially dissolved. ^dCompletely dissolved. ^eBuOH (0.25 mmol).

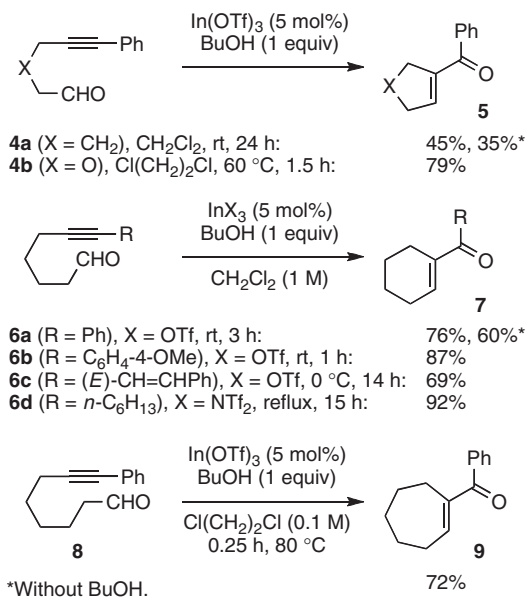
carbon C(3). Combined use of $\text{In}(\text{OTf})_3$ and BuOH enhanced the downfield shift of C(3). These results suggest that $\text{In}(\text{OTf})_3$ should serve as a Lewis acid to activate aldehydes but not as a π -Lewis acid to activate alkynes.⁸

Experiments using BuOD and deuterated phenylacetylene (**1a-d**, >98%*d*) were also carried out to gain more mechanistic insights. The $\text{In}(\text{OTf})_3$ -catalyzed reaction of **1a** with **2a** in the presence of BuOD gave 2-deuterated chalcone (**3aa-d**) with 36% D-content (eq 2). The coupling between **1a-d** and **2a** without BuOH proceeded in low yield with a slight loss of D-content.⁹ Use of BuOH effectively promoted the coupling, however, the product D-content decreased largely (eq 3). Treatment of **3aa-d** (86%*d*) with BuOH (1 equiv) and $\text{In}(\text{OTf})_3$ (5 mol %) at 100 °C for 1 h resulted in no erosion of the D-content. This indicates that the D–H exchange takes place on the reaction pathway to the metathesis product.



The present reaction proceeds probably by two different mechanisms, paths **a** and **b**: the former involves the action of BuOH and the latter is promoted only by In(OTf)₃ (Scheme 1). In both cases, the first step is the In(OTf)₃-promoted addition of an alkyne **1** to an aldehyde **2**, which reversibly forms zwitterionic intermediate **A**. In path **a**, **A** irreversibly reacts with BuOH. The resultant adduct **B** is cyclized to oxetane **C** by intramolecular proton transfer and C–O bond formation. The ring opening of **C** gives the product **3**. In path **b**, **3** is formed by cyclization–cycloreversion of **A** via oxetene **D**. The rate-accelerating effect of BuOH suggests that path **a** should be the major path. The irreversible reaction of **A** with BuOH would lead to the successful coupling. The deuteration with BuOD (eq 2) and the remarkable decrease of D-content with BuOH (eq 3) can be well rationalized by path **a**. The difference between the BuOD-mediated reaction of **1a** and the BuOH-mediated reaction of **1a-d** in the D-content of **3aa-d** is probably due to the presence of path **b** as the minor path.

The In(OTf)₃-catalyzed metathesis reaction was applied to the cyclization of alkynals (Scheme 2).^{3b,3d} The reaction of **4a** in CH₂Cl₂ at room temperature gave the desired product **5a**. The yield decreased without BuOH. Alkynal **4b**, having an ether group, was efficiently cyclized to cyclic ether **5b**. Alkynals **6a–6c** were smoothly cyclized to cyclohexenyl ketones **7a–7c** under mild conditions, while alkynal **6d** was hardly cyclized. Use of



In(NTf₂)₃ instead of In(OTf)₃ effectively promoted the cyclization of **6d** to **7d**. The present reaction was also usable for the construction of 7-membered carbocycle **9**. Thus the InX₃–BuOH catalysis is valuable for the cyclization of flexible alkynals bearing a methylene tether.

In conclusion, we have developed a new catalytic system for the metathesis-type coupling of alkynes with aldehydes. The combined use of indium Lewis acids and BuOH is effective in the inter- and intramolecular coupling.⁴ We have proposed that BuOH cooperatively serves for the C–C bond formation by trapping the unstable intermediate **A**.¹⁰

References and Notes

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- Hanzawa and co-workers have reported that the combined use of SbF₅ (10 mol%) and EtOH (1 equiv) is effective in the tandem alkyne–aldehyde metathesis–Nazarov cyclization, and that SbF₅–EtOH may serve as a protic catalyst. A. Saito, M. Umakoshi, N. Yagyu, Y. Hanzawa, *Org. Lett.* **2008**, *10*, 1783.
- Li and Viswanathan have reported that In(OTf)₃ itself is not effective in the metathesis-type coupling. See ref. 2b.
- The results with other alcohols are as follows. Alcohol (yield of **3aa**/ %): MeOH (60), EtOH (64), *i*-PrOH (64), 1-hexanol (68). Catalytic use of BuOH (0.1 equiv) gave **3aa** in 56% yield.
- The high reactivity of **1f** has been reported in refs. 3a and 3b.
- T. Tsuchimoto, T. Maeda, E. Shirakawa, Y. Kawakami, *Chem. Commun.* **2000**, 1573.
- The loss of D-content may be due to adventitious water or TfOH. They possibly react with intermediate **A** as BuOH does (path **a** in Scheme 1).
- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.