JOC Note

Indium-Catalyzed Highly Efficient Three-Component Coupling of Aldehyde, Alkyne, and Amine via C−H Bond Activation

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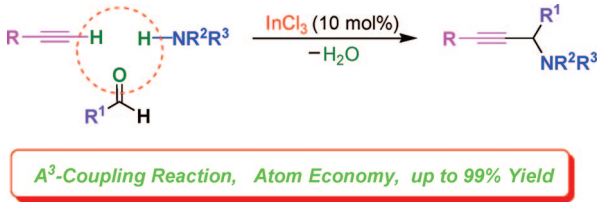

In this paper, indium(III) chloride was found to be a highly effective catalyst for the three-component coupling reactions of aldehydes, alkynes, and amines (A^3-coupling) via C−H activation. The reactions could be applied to both aromatic and aliphatic aldehydes and alkynes. Nearly quantitative yields of the desired products were obtained in most cases. No cocatalyst or activator is required, and water is the only byproduct in the reactions. Furthermore, a tentative mechanism of the $InCl_3$-catalyzed one-pot, three-component coupling of aldehyde, alkyne, and amine is proposed.

Multicomponent coupling reactions (MCRs) are a powerful synthetic tool to access complex structures from simple precursors via a one-pot procedure, and in general, those reported exhibit high atom economy and selectivity.[1] Three-component coupling of an aldehyde, an alkyne, and an amine (A^3-coupling) is one of the best examples of such a process, and this transformation has received much attention in recent years.[2] The resultant propargylamines obtained from A^3-coupling reactions are frequent skeletons[3] and synthetically versatile key intermediates[4] for the preparation of many nitrogen-containing biologically active compounds such as β-lactams, oxotremorine analogues, conformationally restricted peptides, isosteres, natural products, and therapeutic drug molecules.[3b,5] Classical methods for the preparation of propargylamines have usually exploited the relatively high acidity of a terminal acetylenic C−H bond to form alkynylmetal reagents by reaction with strong bases such as butyllithium,[6a] organomagnesium compounds,[6b] or LDA[7] in a separate step. Unfortunately, these reagents are required in stoichiometric quantities, are highly moisture sensitive, and require strictly controlled reaction conditions.

In recent years, enormous progress has been made in expanding the scope of the direct addition of alkynes to carbon−nitrogen double bonds either from prepared imines or from aldehydes and amines in one-pot procedure by several noble transition-metal catalysts via C−H activation of terminal alkynes. Ag^I salts,[8] Au^I/Au^{III} salts,[2,9] Au^{III}−salen complexes,[10] Cu^I salts,[11] Ir complexes,[12] Hg_2Cl_2,[13] and Cu/Ru^{II} bimetallic system[14] have all been used for this reaction under homogeneous conditions, where water is the only theoretical byproduct. Recently, Au^I, Ag^I, and Cu^I in ionic liquids and supported Au^{III}, Ag^I, and Cu^I were successfully used to catalyze three-component coupling reactions under heterogeneous reaction conditions with recyclability and reusability of the transition-metal catalysts.[15]

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(1) (a) For multicomponent reactions, see: *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley: Weinheim, 2005. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (c) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647. (d) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366. (e) Ugi, I.; Steinbrueckner, C. *Chem. Ber.* **1961**, *94*, 2802. (f) Strecker, A. *Ann. Chem.* **1850**, *75*, 27. (g) Mannich, C.; Kosche, W. *Arch. Pharm.* **1912**, *250*, 647. (h) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474.

(2) Wei, C.; Zhang, L.; Li, C. J. *Synlett* **2004**, 1472, and references cited therein.

(3) (a) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.

(4) (a) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999. (b) Jenmalm, A.; Berts, W.; Li, Y. L.; Luthman, K.; Csoregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, *59*, 1139.

(5) (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Naota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599.

(6) (a) Wakefield, B. J. *Organolithium Methods in Organic Synthesis*; Academic Press: London, 1988; Chapter 3, p 32. (b) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; Chapter 3, p 46.

(7) (a) Harada, T.; Fujiwara, T.; Iwazaki, K.; Oku, A. *Org. Lett.* **2000**, *2*, 1855. (b) Rosas, N.; Sharma, P.; Alvarez, C.; Gomez, E.; Gutierrez, Y.; Mendez, M.; Toscano, R. A.; Maldonado, L. A. *Tetrahedron Lett.* **2003**, *44*, 8019. (c) Ding, C.-H.; Chen, D.-D.; Luo, Z.-B.; Dai, L.-X.; Hou, X.-L. *Synlett* **2006**, 1272.

(8) Wei, C.; Li, Z.; Li, C. J. *Org. Lett.* **2003**, *5*, 4473.

(9) Wei, C.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.

(10) Lo, V. K. Y.; Liu, Y.; Wong, M. K.; Che, C. M. *Org. Lett.* **2006**, *8*, 1529.

(11) (a) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A. *Org. Lett.* **2004**, *6*, 1001. (b) Syeda, H. Z. S.; Halder, R.; Karla, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485. (c) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 676. For enantioselective syntheses of propargylamines through CuI-catalyzed one-pot, three-component coupling reactions of aldehydes, alkynes, and amines, see: (d) Wei, C.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (e) Wei, C.; Mague, J. T.; Li, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749. (f) Gommarman, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed* **2003**, *42*, 5763. (g) Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F. *J. Mol. Catal. A: Chem.* **2006**, *260*, 128. (h) Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380. (i) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405.

(12) (a) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319. (b) Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2534. (c) Sakaguchi, S.; Mizuta, T.; Furuwan, M.; Kubo, T.; Ishii, Y. *Chem. Commun* **2004**, 1638.

(13) Li, P.; Wang, L. *Chin. J. Chem.* **2005**, *23*, 1076.

(14) Li, C. J.; Wei, C. *Chem. Commun.* **2002**, *3*, 268.

(15) (a) Li, Z.; Wei, C.; Chen, L.; Varma, R. S.; Li, C. J. *Tetrahedron Lett.* **2004**, *45*, 2443. (b) Park, S. B.; Alper, H. *Chem. Commun.* **2005**, *10*, 1315. (c) Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Sreedhar, B. *Tetrahedron Lett.* **2004**, *45*, 7319. (d) Kantam, M. L.; Prakash, B. V.; Reddy, C. R. V.; Sreedhar, B. *Synlett* **2005**, 2329. (e) Reddy, K. M.; Babu, N. S.; Prasad, P. S. S.; Lingaiah, N. *Tetrahedron Lett.* **2006**, *47*, 7563. (f) Zhang, X.; Corma, A. *Angew. Chem., Int. Ed* **2008**, *47*, 4358. (g) Li, P.; Wang, L. *Tetrahedron* **2007**, *63*, 5455. (h) Wang, M.; Li, P.; Wang, L. *Eur. J. Org. Chem.* **2008**, 2255.

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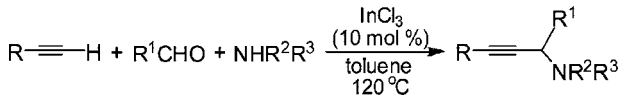
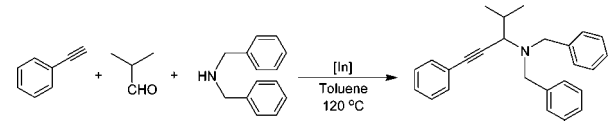
SCHEME 1



The utility of indium(III) salts as Lewis acids in organic synthesis has received a great deal of interest due to their relatively low toxicity, stability in air and water, recyclability, operational simplicity, and strong tolerance to oxygen- and nitrogen-containing substrates and functional groups.[16] Their potential as Lewis acid catalysts for fundamental reactions, such as the Diels−Alder,[17] Friedel−Crafts,[18] Mukaiyama aldol,[19] and Sakurai−Hosomi allylation reactions,[20] has been extensively investigated.[21] However, indium-catalyzed three-component coupling reactions of aldehydes, terminal alkynes, and amines has not so far been described. As a part of our program aiming to develop selective and environmental friendly methods for the preparation of fine chemicals and in continuation of our interest in exploring novel synthetic strategies for the synthesis of propargylamines via activation of terminal alkynes,[15g,h,22] herein we report $InCl_3$ as an inexpensive, high-yielding catalyst for the three-component coupling of aldehydes, alkynes, and amines (A^3-coupling) without any cocatalyst or activator. The reactions generated the corresponding products in nearly quantitative yields in most cases. This method provided a wide range of substrate applicability and could be applied to both aromatic and aliphatic aldehydes and alkynes (Scheme 1).

At the outset, the catalytic activity of a variety of indium salts were examined in a model reaction of phenylacetylene, isobutyraldehyde, and dibenzylamine in toluene under an argon atmosphere at 120 °C for 20 h, and the results are summarized in Table 1. To our delight, the three-component coupling reaction proceeded smoothly and generated the desired product propargylamine in 98% yield, representing one of the best results when 10 mol % of $InCl_3$ was used as catalyst without any cocatalyst or activator (Table 1, entry 1). Other indium salts, such as $InBr_3$, InI_3, $In(CF_3SO_3)_3$, and $In(CH_3COO)_3$, were inferior and generated the desired product in 53, 78, 71, and 72% yields, respectively (Table 1, entries 2−5). In(I) salts seemed slightly better than In(III) salts, and the corresponding product was obtained in 99% yield (Table 1, entry 6). Considering that $InCl_3$ is relatively cheap compared to other indium salts and the most effective, it was therefore chosen as the catalyst for the following experiments. With respect to the catalyst loading, 10 mol % of $InCl_3$ was found to be optimal. When 5 mol % of $InCl_3$ was used, the reaction did not go to completion, and excellent yield of the product was obtained as the reaction time was prolonged (Table 1, entries 7 and 8). However, no significant improvement was observed with 20 mol % of $InCl_3$ (Table 1, entry 9).

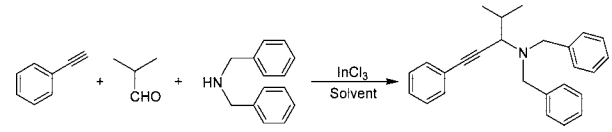
TABLE 1. Screening of Catalysts for A^3-Coupling Reactions[a]



entry	indium source	yield[b] (%)
1	$InCl_3$	98
2	$InBr_3$	53
3	InI_3	78
4	$In(CF_3SO_3)_3$	71
5	$In(CH_3COO)_3$	72
6	InCl	99
7[c]	$InCl_3$	78
8[d]	$InCl_3$	95
9[e]	$InCl_3$	98

[a] Reaction conditions: phenylacetylene (1.2 equiv), isobutyraldehyde (1.2 equiv), dibenzylamine (1.0 equiv), indium source (0.10 equiv), toluene (1.0 mL·mmol^{-1}), 120 °C, under argon, 20 h. [b] Yield of isolated product after flash chromatography. [c] In the present of $InCl_3$ (0.05 equiv). [d] In the present of $InCl_3$ (0.05 equiv) for 36 h. [e] In the present of $InCl_3$ (0.20 equiv).

TABLE 2. Effect of Solvent on $InCl_3$-Catalyzed A^3-Coupling Reactions[a]



entry	solvent/T (°C)	yield[b] (%)
1	toluene/120	98
2	benzene/80	83
3	1,4-dioxane/100	81
4	DCE/83	87
5	CH_3CN/82	78
6	C_2H_5OH/78	50
7	CH_3OH/68	56
8	H_2O/100	65
9	PEG-400/120	53
10	DMA/120	0
11	DMSO/120	0
12	DMF/120	0
13	$BmimBF_4$/120	0

[a] Reaction conditions: phenylacetylene (1.2 equiv), isobutyraldehyde (1.2 equiv), dibenzylamine (1.0 equiv), $InCl_3$ (0.10 equiv), solvent (1.0 mL·mmol^{-1}) at the temperature indicated in Table 2, under argon, 20 h. [b] Yield of isolated product after flash chromatography.

We next screened the effect of solvent on A^3-coupling of model substrates by using 10 mol % of $InCl_3$ as catalyst at 120 °C, and the nature of solvent significantly affects the reaction (Table 2). Among the solvents tested in Table 2, toluene was the most suitable reaction medium for the A^3-coupling reaction (Table 2, entry 1). Benzene, 1,4-dioxane, 1,2-dichloroethane (DCE), and CH_3CN were inferior and generated the corresponding products in 83, 81, 87, and 78% yields, respectively (Table 2, entries 2−5), whereas C_2H_5OH, CH_3OH, H_2O, and PEG-400 afforded moderate yields of the desired products (Table 2,

(16) Reviews for indium Lewis acids: (a) Frost, C. G.; Chauhan, K. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. (b) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Curr. Org. Chem.* **2003**, *7*, 1661. (c) Frost, C. G.; Hartley, J. P. *Mini-Rev. Org. Chem.* **2004**, *1*, 1. (d) Zhang, Z.-H. *Synlett* **2005**, 711.

(17) (a) Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539. (b) Babu, G.; Perumal, P. T. *Tetrahedron Lett.* **1998**, *39*, 3225.

(18) Miyai, T.; Onishi, Y.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 6291.

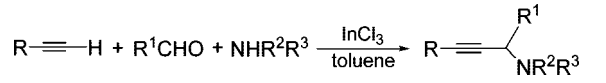
(19) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998**, *39*, 323.

(20) (a) Friestad, G. K.; Korapala, C. S.; Ding, H. *J. Org. Chem.* **2006**, *71*, 281. (b) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578.

(21) For allylation of carbonyl compounds with allyltributylstannanes, see: (a) Teo, Y.-U.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743. (b) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (c) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920. For other reactions, see: (d) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365. (e) Yanada, R.; Obika, S.; Kobayashi, Y.; Inokuma, T.; Oyama, M.; Yanada, K.; Takemoto, Y. *Adv. Synth. Catal.* **2005**, *347*, 1632. (f) Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825. (g) Dobbs, A. P.; Guesné, S. J. J.; Martinović, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880. (h) Onishi, Y.; Ogawa, D.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13690. (i) Cho, Y. S.; Kim, H. Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M. H. *Org. Lett.* **2002**, *4*, 2025. (j) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741.

(22) (a) Li, P.; Wang, L.; Zhang, Y.; Wang, M. *Tetrahedron Lett.* **2008**, *49*, 6650. (b) Li, P.; Zhang, Y.; Wang, L. *Chem.—Eur. J.* **2009**, *15*, 2045.

TABLE 3. $InCl_3$-Catalyzed A^3-Coupling Reactions[a]



entry	R	R^1	R^2, R^3	yield[b] (%)
1	C_6H_5	i-C_3H_7	2 ($C_6H_5CH_2$)	98
2	p-$CH_3C_6H_4$	i-C_3H_7	2 ($C_6H_5CH_2$)	99
3	p-FC_6H_4	i-C_3H_7	2 ($C_6H_5CH_2$)	97
4	p-ClC_6H_4	i-C_3H_7	2 ($C_6H_5CH_2$)	98
5	p-$C_6H_5C_6H_4$	i-C_3H_7	2 ($C_6H_5CH_2$)	96
6	n-C_8H_{17}	i-C_3H_7	2 ($C_6H_5CH_2$)	89
7	n-C_6H_{13}	i-C_3H_7	2 ($C_6H_5CH_2$)	87
8	C_6H_5	n-C_3H_7	2 ($C_6H_5CH_2$)	95
9	C_6H_5	i-C_4H_9	2 ($C_6H_5CH_2$)	94
10	C_6H_5	H	2 ($C_6H_5CH_2$)	99
11	C_6H_5	c-C_6H_{11}	2 ($C_6H_5CH_2$)	98
12	C_6H_5	C_6H_5	2 ($C_6H_5CH_2$)	99[c]
13	C_6H_5	p-$CH_3C_6H_4$	2 ($C_6H_5CH_2$)	92[c]
14	C_6H_5	p-ClC_6H_4	2 ($C_6H_5CH_2$)	83[c]
15	C_6H_5	i-C_3H_7	$(CH_2)_5$	76
16	C_6H_5	i-C_3H_7	$(CH_2)_2O(CH_2)_2$	85
17	C_6H_5	H	2 (i-C_3H_7)	78
18	C_6H_5	H	$(CH_2)_5$	80
19	C_6H_5	H	2 (c-C_6H_{11})	68
20	C_6H_5	C_6H_5	$(CH_2)_5$	96[c]
21	C_6H_5	p-$CH_3C_6H_4$	$(CH_2)_5$	97[c]
22	C_6H_5	p-$CH_3OC_6H_4$	$(CH_2)_5$	90[c]
23	C_6H_5	p-ClC_6H_4	$(CH_2)_5$	87[c]

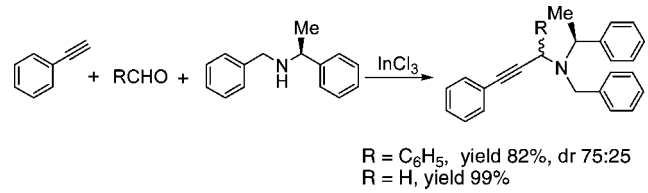
[a] Reaction conditions: amine (1.0 mmol), aldehyde (1.2 mmol), alkyne (1.2 mmol), $InCl_3$ (0.10 mmol), toluene (1.0 mL), 120 °C, under argon, 20 h. [b] Yield of isolated product after flash chromatography. [c] In the present of 4 Å molecular sieves (100 mg), which are thought to scavenge water.

entries 6−9). Unfortunately, no desired product was isolated when the reactions were carried out in *N*,*N*-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BmimBF_4$) (Table 2, entries 10−13). During the course of our further optimization of the reaction conditions, the reaction was generally completed within 20 h when it was performed at 120 °C by using 10 mol % of $InCl_3$ in toluene without any cocatalyst or activator.

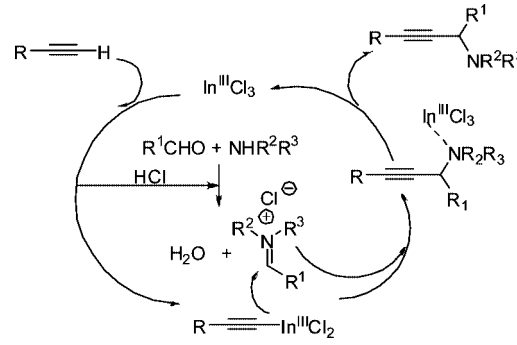
On the basis of the previously optimized reaction conditions, the scope of this three-component coupling reaction was evaluated. The results are outlined in Table 3. At the beginning of the investigation into the alkyne substrate scope, isobutyraldehyde and dibenzylamine were used as model substrates and a variety of alkynes were examined for the A^3-coupling reactions (Table 3, entries 1−7). As can be seen from Table 3, aromatic alkynes were often much more reactive than aliphatic alkynes. Aromatic alkynes, with either electron-donating or electron-withdrawing groups attached to the benzene rings, were able to undergo three-component coupling smoothly and generated the corresponding products in excellent yields (Table 3, entries 1−5). Fortunately, aliphatic alkynes also gave the corresponding propargylamines in good yields (Table 3, entries 6 and 7).

To expand the scope of aldehyde substrates, a combination of phenylacetylene−dibenzylamine−aldehydes was chosen, and various aldehydes were surveyed. Aliphatic aldehydes, acyclic or cyclic, such as isobutyraldehyde, *n*-butyraldehyde, isovaleraldehyde, cyclohexanecarboxaldehyde, and formaldehyde, displayed high reactivity under the optimized reaction conditions and generate the desired products in high yields (Table 3, entries 1, and 8−11). Fortunately, aromatic aldehydes with both electron-donating and electron-withdrawing functional groups, such as methyl and chloro groups, afforded the corresponding products in good yields in the presence of 4 Å molecular sieves (Table 3, entries 12−14 and 20−23). In the absence of 4 Å molecular sieves, the yields were moderate.

SCHEME 2



SCHEME 3. Possible Mechanism of $InCl_3$-Catalyzed Three-Component Coupling of Aldehyde, Alkyne, and Amine



To expand the scope of amine substrates, phenylacetylene was used as a model substrate and various amines with different aldehydes were examined (Table 3, entries 1 and 15−23). The results indicated that cyclic, heterocyclic, and acyclic secondary aliphatic amines gave excellent yields of products under the standard reaction conditions. However, no A^3-reaction product was isolated when an aromatic secondary amine, such as *N*-benzylaniline or *N*-methylaniline, was served as amine substrate.

Considering that chiral propargylamines are widely present in many important bioactive compounds, we subsequently investigated a novel substrate-controlled asymmetric indium-catalyzed A^3-coupling. A chiral amine, (*S*)-*N*-benzyl-1-phenylethylamine, was selected for examination using benzaldehyde and phenylacetylene as model substrates, as depicted in Scheme 2. It was interesting to note that (*S*)-*N*-benzyl-1-phenylethylamine exhibited good diastereoselectivity (75:25), and a very high yield (99%) of the product was isolated when an A^3-coupling reaction of phenylacetylene, formaldehyde, and (*S*)-*N*-benzyl-1-phenylethylamine was carried out under the present reaction conditions.

A tentative mechanism of the $InCl_3$-catalyzed one-pot, three-component coupling of aldehyde, alkyne, and amine is proposed in Scheme 3. The catalyst $InCl_3$ would be first reacted with terminal alkyne to form a stable In^{III} alkynyl−ate complex and release HCl.[23] When PhC≡C$InCl_2$ prepared according to the literature[23] was used instead of PhC≡CH to react with immonium salt in the absence of additional $InCl_3$ at 120 °C in toluene, 97% yield of the desired product was isolated. On the other hand, we hypothesize that the generated HCl accelerates the formation of immonium salt from aldehyde and secondary amine,[24] and $InCl_3$ as a Lewis acid plays a role in increasing

(23) Takami, K.; Usugi, S. I.; Yorimitsu, H.; Oshima, K. *Synthesis* **2005**, 824.

the electrophilic character of the starting aldehyde and stabilizing the immonium salt by the coordination of oxygen or nitrogen lone electron pair with In(III).[25] The resulting indium acetylide intermediate subsequently reacted with immonium salt generated in situ to give the corresponding propargylamine and regenerate In^{III} catalyst.

In conclusion, a highly efficient indium-catalyzed three-component coupling of aldehydes, alkynes, and amines via C−H bond activation has been achieved in toluene. The process was simple and generated a diverse range of propargylamines in excellent yields. The reaction is applicable to both aromatic and aliphatic aldehydes and alkynes. Water is the only byproduct in this novel three-component reaction. The scope, mechanism, stereoselectivity, and synthetic applications of this reaction are under investigation.

Experimental Section

General Procedure for the Indium-Catalyzed Three-Component Coupling Reactions. In argon atmosphere, a sealable reaction tube with a Teflon-coated screw cap equipped with a magnetic stir bar was charged with alkyne (1.2 mmol), aldehyde (1.2 mmol), amine (1.0 mmol), $InCl_3$ (0.1 mmol), and toluene (1.0 mL). The reaction vessel was placed in an oil bath at 120 °C, the mixture was stirred for 20 h and then cooled to room temperature, the solvent was filtered and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (eluant: hexane/ethyl acetate) to give the corresponding A^3-coupling product.

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Supporting Information Available: Representative experimental procedure, analytical data, and copies of ^1H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) (a) Risch, N.; Arend, M. *Houben-Weyl*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds: Thieme: Stuttgart, 1995; Vol. E21b, p 1925. (b) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: London, 2005; p 274. (c) Benkovic, S. J.; Benkovic, P. A.; Comfort, D. R. *J. Am. Chem. Soc.* **1969**, *91*, 1860. (d) Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1963**, *28*, 3021.
(25) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.