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A New Entry in Catalytic Alkynylation of Aldehydes and Ketones: Dual Activation of Soft Nucleophiles and Hard Electrophiles by an Indium(III) Catalyst

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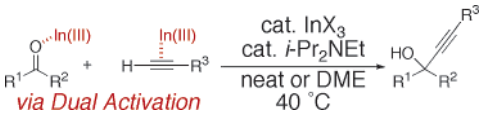
ABSTRACT



A new entry in catalytic alkynylation of carbonyl compounds was developed in which dual activation of both soft nucleophiles (terminal alkynes) and hard electrophiles (aldehydes and ketones) is achieved using an indium(III) catalyst. Preliminary mechanistic studies using in situ IR and NMR spectroscopic analysis are also discussed.

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.[1] Stoichiometric amounts of strong bases such as organolithium, organomagnesium, or dialkylzinc[2] 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 step for metal acetylide preparation make it difficult to achieve an atom-economical process with high total efficiency.

The in situ catalytic generation of metal nucleophiles and their use in carbon−carbon bond-forming reactions such as the direct-aldol reaction[3,4] is currently a major interest in organic synthesis. Thus, the development of an alkynylation of carbonyl compounds using a *catalytic amount of metal* is in high demand. Quite recently, Carreira and co-workers developed an efficient method for in situ generation of zinc acetylide from terminal alkynes and their addition to carbonyl compounds using $Zn(OTf)_2$ and an amine base[5,6] via π-complex formation.[7] They successfully applied this chemistry to catalytic enantioselective alkynylation of aliphatic aldehydes promoted by $Zn(OTf)_2$ (20 mol %), *N*-methyl ephe-

(1) For a recent review, see: Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095.

(2) (a) For a review, see: Pu, L. *Tetrahedron* **2003**, *59*, 9873. See also ref 1. For recent representative examples, see: (b) Gao, G.; Xie, R.-G.; Pu, L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5417. (c) Li, Z.-B.; Pu, L. *Org. Lett.* **2004**, *6*, 1065. (d) Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193. (e) Dahmen, S. *Org. Lett.* **2004**, *6*, 2113. (f) Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427. (g) Kang, Y.-F.; Liu, L.; Wang, R.; Yan, W.-J.; Zhou, Y.-F. *Tetrahedron: Asymmetry* **2004**, *15*, 3155. For examples of alkynylation of ketones, see: (h) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895. (i) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057. (j) Saito, B.; Katsuki, T. *Synlett* **2004**, 1557. (k) Cozzi, P. G.; Alesi, S. *Chem. Commun.* **2004**, 2448. (l) Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z. *Org. Lett.* **2004**, *6*, 4147. (m) Liu, L.; Wang, R.; Kang, Y.-F.; Chen, C.; Xu, Z.-Q.; Zhou, Y.-F.; Ni, M.; Cai, H.-Q.; Gong, M.-Z. *J. Org. Chem.* **2005**, *70*, 1084.

(3) For reviews, see: (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (b) List, B. *Tetrahedron* **2002**, *58*, 5573.

(4) (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (b) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (c) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566. (d) *Multimetallic Catalysts in Organic Synthesis*; Shibasaki, M., Yamamoto, Y., Eds.; Wiley-VCH: Weinheim, 2004.

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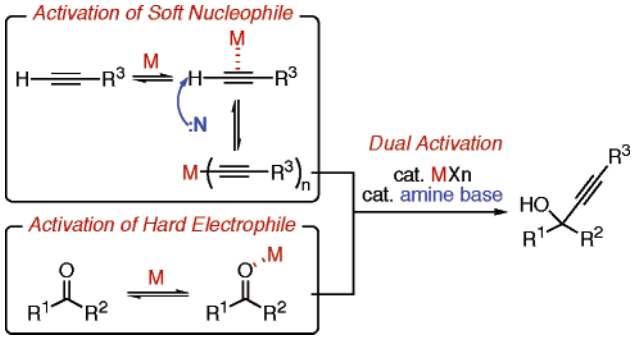
drine (22 mol %), and Et_3N (50 mol %) just by increasing the temperature to 60 °C.[5c] Another catalytic alkynylation of aldehydes and ketones using a *catalytic* amount of strong hydroxide, alkoxide, or phosphazene base in polar solvents has also been reported.[8] Although the alkynylation of carbonyl compounds is realized in these two systems using only a catalytic amount of metal, the substrate generality is quite limited. For example, in both systems, aromatic aldehydes cannot be used due to the side reaction (Carreira reported that the Cannizzaro reaction is a serious side reaction[5c]). Moreover, in each case, broad generality is lacking, due mainly to high temperature[5c] or strongly basic conditions.[8] Thus, there remains much room to develop catalytic alkynylation of various carbonyl compounds under mild conditions. Herein, we report a new entry in catalytic alkynylation of aliphatic/aromatic aldehydes and ketones using indium(III) salt and *i*-Pr_2NEt. Preliminary mechanistic studies using in situ IR and NMR spectroscopic analysis are also discussed.

Our group has developed various bifunctional catalysts[4] 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 nucleophiles (terminal alkynes) and hard electrophiles (carbonyl compounds) is very important. For example, heterobimetallic catalysts, including soft transition metals and hard Lewis acidic metals, might be suitable for this purpose.[9] The rational design of such a bimetallic catalyst system, however, is difficult. Therefore, we focused on dual activation by one metal, which should have both Lewis acidity to carbonyl compounds and π-coordination ability to alkynes. Indium(III) salts are efficient Lewis acids for carbonyl compounds and, in fact, are utilized for a wide range of reactions.[10] Quite recently, indium(III) salts have emerged as effective activators of alkynyl groups in cross-coupling reactions, etc.[11] These features prompted us 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 in Combination with a Catalytic Amount of Metal Salt and Amine Base



Using benzaldehyde (**1a**) or cyclohexanecarboxaldehyde (**1k**) with phenylacetylene (**2a**) as representative substrates, we screened various indium(III) salts and reaction conditions; the combination of $InBr_3$ with *i*-Pr_2NEt provided the optimal reaction efficiency in the alkynylation of aldehydes.[12] The scope and limitations using various aldehydes are summarized in Table 1. Under the optimized reaction conditions (10 mol % $InBr_3$, 20 mol % *i*-Pr_2NEt, and 2 equiv of terminal alkynes at 40 °C without solvent), a variety of aromatic aldehydes were smoothly converted to the corresponding propargylic alcohols **3**. Benzaldehyde derivatives having both electron-donating substituents (entries 2 and 3) and electron-withdrawing substituents (entries 4−9) gave the products in satisfactory yields. The reaction with 1-naphthaldehyde (**1i**) (entry 10) and 3-thiophenecarboxaldehyde (**1j**) (entry 11) also proceeded well. The reaction with aliphatic aldehyde **1k** had

(5) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373 (c) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (d) Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843. See also: (e) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245.

(6) For the other examples using stoichiometric amounts of metal salts, see the following. $Sn(OTf)_2$: (a) Yamaguchi, M.; Hayashi, A.; Minami, T. *J. Org. Chem.* **1991**, *56*, 4091. (b) Yamaguchi, M.; Hayashi, A.; Hirama, M. *Chem. Lett.* **1992**, 2479. GaI_3: (c) Han, Y.; Huang, Y.-Z. *Tetrahedron Lett.* **1995**, *36*, 7277. $ZnCl_2$: (d) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 8323. $InBr_3$: (e) Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2003**, *44*, 4171.

(7) Although late transition metals such as Cu(I), Ag(I), and Au(I) are effective for the formation of metal acetylides in a similar way as Zn(II), they can be utilized for alkynylation of C═N compounds such as imines, but not for alkynylation of carbonyl coumpunds. For a review, see: (a) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472. For representative examples of Cu, see: (b) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (c) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (d) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (e) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107. Ag: (f) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473. (g) Ji, J.-X.; Au-Yeung, T. T.-L.; Wu, J.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 42. Au: (h) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. Ir: (i) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319. (j) Fischer, C.; Carreira, E. M. *Synthesis* **2004**, 1497. Ru−Cu: (k) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268. For related works, see: (l) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (m) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997.

(8) (a) Babler, J. H.; Liptak, V. P.; Phan, N. *J. Org. Chem.* **1996**, *61*, 416. (b) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463. (c) Miyamoto, H.; Yasaka, S.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 185. (d) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* **2003**, *68*, 3702. (e) Imahori, T.; Hori, C.; Yamamoto, Y. *Adv. Synth. Catal.* **2004**, *346*, 1090.

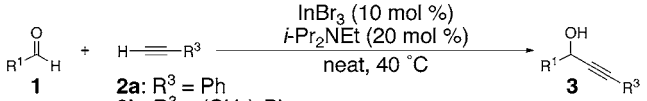
(9) Li and Wei reported the combination of $In(OAc)_3$ and $RuCl_3$ as a well-defined catalyst for alkynylation of aldehydes, although the chemical yields were moderate (27−62%, 12 entries) except for one entry (94%). They proposed that the C−H bond of alkyne is activated by the ruthenium catalyst and aldehyde is activated by the indium catalyst: Wei, C.; Li, C.-J. *Green Chem.* **2002**, *4*, 39.

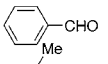
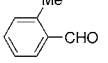
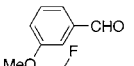
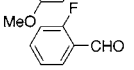
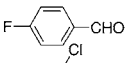
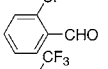
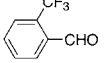
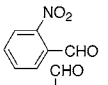
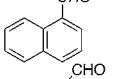
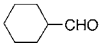
(10) (a) For a review, see: Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. For recent representative examples, see: (b) Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042. (c) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (d) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206 and references therein.

(11) For examples of catalytic activation of alkynes by In(III), see: (a) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573. (b) Tsuchimoto, T.; Hatanaka, K.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2003**, 2454. (c) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002. (d) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527. See also ref 6e.

(12) See Supporting Information for details.

Table 1. $InBr_3$-Catalyzed Alkynylation of Aldehydes



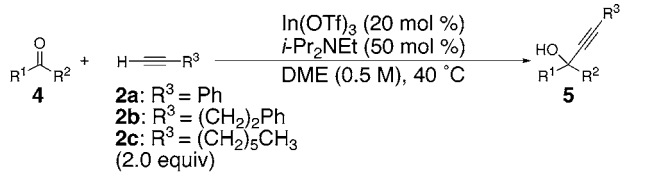
entry	aldehyde		alkyne	time (h)	yield (%)
1		**1a**	H—≡—Ph	44	73
2		**1b**	H—≡—Ph	48	88
3		**1c**	H—≡—Ph	44	63
4		**1d**	H—≡—Ph	24	86
5[a]		**1e**	H—≡—Ph	22	73
6		**1f**	H—≡—Ph	5	93
7		**1g**	H—≡—Ph	10	98
8			H—≡—$(CH_2)_2$Ph	42	75
9		**1h**	H—≡—Ph	10	99
10		**1i**	H—≡—Ph	24	82
11		**1j**	H—≡—Ph	48	62
12[a]		**1k**	H—≡—Ph	10	84

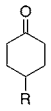
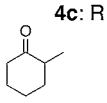
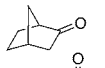
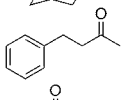
[a] DME was used as a solvent (5.0 M).

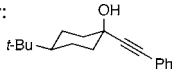
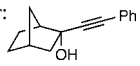
high reactivity and afforded the product **3ka** in 84% yield, although other aliphatic aldehydes gave unsatisfactory results due to the self-condensation of aldehydes (aldehydes with a primary alkyl group) and low reactivity (aldehydes with a tertiary alkyl group). It is worth noting that the reaction was performed under neat or highly concentrated (5.0 M) conditions with minimal waste, making this process desirable in terms of practicality.[5c] Moreover, to the best of our knowledge, this is the most effective system for the catalytic alkynylation of aromatic aldehydes.

Next, we examined the alkynylation of ketones using cyclohexanone (**4a**) with **2a** as model substrates. Under the optimized conditions for aldehydes, however, the desired product **5aa** was obtained in very low yield (ca. 5% yield). Changing the indium source from $InBr_3$ to $In(OTf)_3$ (20 mol %) greatly improved the reactivity to afford **5aa** in 90% yield after 24 h. Even when the catalyst loading was lowered to 10 mol %, the isolated yield was 92% after 63 h. Under the optimized reaction conditions (20 mol % $In(OTf)_3$ and 50 mol % Et_3N at 40 °C in DME), the cyclohexanone derivatives (entries 5−7) as well as bicyclic ketone (entry 8) were successfully converted to the tertiary propargylic alcohols **5**. Despite the high degree of instability of the corresponding tertiary alcohol of acyclic aliphatic ketones (entries 9 and 10) under basic conditions, the present catalytic reaction successfully provided the products in moderate yields, overcoming the retroreaction problem. The fact that even such a challenging substrate gave greater than 60% chemical yield without trapping by stoichiometric metals was very encouraging. Furthermore, less reactive alkylacetylenes (much less acidic than **2a**) were also applicable to the alkynylation of an aldehyde (Table 1, entry 8) as well as a ketone (Table 2, entries 3 and 4). In general, under the

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



entry	ketone		alkyne	time (h)	yield (%)
1		**4a**: R = H	H—≡—Ph	24	90
2[a]			H—≡—Ph	63	92
3[b]			H—≡—$(CH_2)_2$Ph	48	85
4[b]			H—≡—$(CH_2)_5CH_3$	48	74
5		**4b**: R = Me	H—≡—Ph	24	90 (dr = 1.3:1)
6		**4c**: R = *t*-Bu	H—≡—Ph	60	94[d] (dr = 2:1)
7		**4d**	H—≡—Ph	10	85 (dr = 1.1:1)
8[b]		**4e**	H—≡—Ph	48	58[e] (dr = 5.2:1)
9[b,c]		**4f**	H—≡—Ph	48	61
10[b,c]		**4g**	H—≡—Ph	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] Major isomer:  [e] Major isomer: 

optimized conditions shown in Tables 1 and 2, side reactions were effectively suppressed; thus, the unreacted carbonyl compounds were recovered in reasonable yield.

The success of this catalytic reaction can be attributed to the dual activation of the alkyne and carbonyl compound. To verify our hypothesis (shown in Scheme 1), we performed in situ IR[5d] and NMR spectroscopic studies. First, to gain precise information about the activation of alkyne, in situ IR spectra were measured as follows (Figure 1); the background was measured in the presence of $InBr_3$ and 2 equiv of *i*-Pr_2NEt in DME (similar to the reaction conditions for aldehydes). When 1 equiv of phenylacetylene (**2a**) was added to the above mixture, there was a signal at 3246 cm^{-1} corresponding to the C−H stretch of the alkyne,[13] and this signal disappeared in less than 1 min. On the other hand,

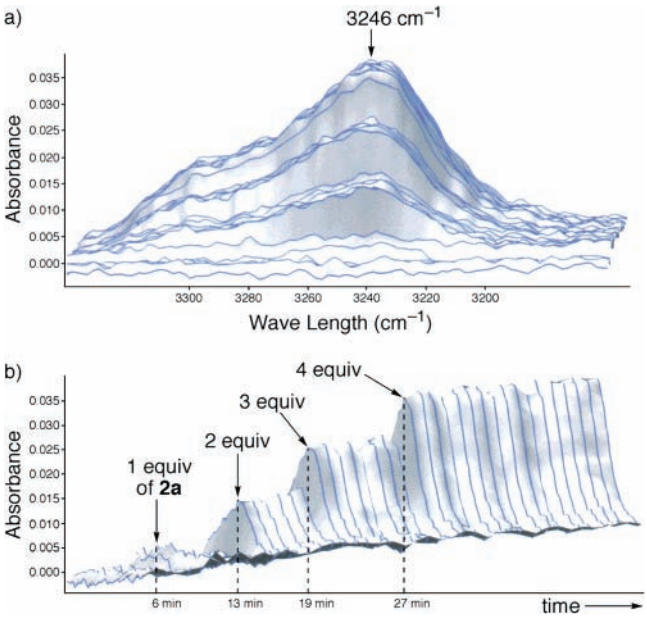


Figure 1. In situ IR study of the successive addition of phenylacetylene (**2a**) to $InBr_3$ and *i*-Pr_2NEt in DME: (a) C−H stretch signal of **2a** and (b) time course of the successive addition (1−4 equiv of phenylacetylene) at 3246 cm^{-1}.

when 1−3 equiv of **2a** was added (total of 2−4 equiv), the absorbance at 3246 cm^{-1} increased with each addition. Moreover, in the absence of $InBr_3$, the signal corresponding to the C−H stretch of the alkyne did not disappear. These results suggested that $InBr_3$ activated the terminal alkyne and that the indium monoacetylide species was formed.[14] Next, to confirm the activation of the carbonyl compound by Lewis acidic indium(III) salt,[10] NMR spectroscopic analysis was performed using $InBr_3$. The shift of the peak corresponding to the aldehyde proton (in the ^1H NMR spectrum) and the carbonyl carbon (in the ^{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**),[12] indicating the activation of the carbonyl compound by coordination to the indium(III) species.

In summary, we developed a new catalytic alkynylation of aldehydes and ketones promoted by the combination of indium(III) salts and *i*-Pr_2NEt. 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. Reactivity and substrate generality might be improved by appropriate ligand choice or further optimization of the reaction conditions. Application to enantioselective variants is ongoing.

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Supporting Information Available: Experimental procedures, characterization of the products, and other detailed results and discussions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) This signal disappeared when phenylacetylene was treated with EtMgBr in DME. See ref 5d.

(14) When a similar experiment was performed using $In(OTf)_3$, formation of indium diacetylide species was implied. For details, see Supporting Information.