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$InBr_3$-catalyzed direct alkynylation of nitrones with terminal alkynes: an efficient synthesis of *N*-hydroxy-propargyl amines

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ABSTRACT

An $InBr_3$-catalyzed direct and efficient alkynylation of nitrones with terminal alkynes was developed. The process enables practical synthesis of a wide range of synthetically useful *N*-hydroxy-propargyl amine derivatives in good yields under mild conditions. The application of this method to optically active propargylic *N*-hydroxyamines syntheses was also described. With chiral nitrones, good diastereoselectivities were obtained. Moreover, the first chiral indium(III) complex-catalyzed asymmetric alkynylation of nitrone was achieved with moderate enantioselectivity.

The catalytic in situ generation of alkynilides and their use in carbon–carbon bond-forming processes are currently of great interest because of the atom economy and high efficiency for preparation of synthetically very useful propargylic compounds.[1–4] Important progress has been made by using various transition-metal catalysts, particularly with easily available zinc and copper salts.[2,3] Carreira and co-workers documented the pioneering work of asymmetric addition of terminal alkynes to aldehydes and nitrones in the presence of catalytic amount of $Zn(OTf)_2$ and tertiary amine.[2a–d] In the same way, via π-complexes formation with further deprotonation, copper[3] and other transition metal[4] acetylides could be generated and subsequently submitted to carbonyls and imines to give the corresponding propargylic adducts. In the past several years, indium(III) salts[5] have also attracted considerable attention of organic chemists in the field because of its remarkable effectivity in activation of alkynes,[6–8] great functional group tolerance, high stability, and low toxicity. Sakai and Konakahara have reported an indium bromide-promoted process in Et_2O for the mild addition of terminal alkynes to aldehydes and acetals,[7] however, stoichiometric amount of indium salt had to be used. Quite recently, Shibasaki and co-workers successfully developed its catalytic version for alkynylation of carbonyl compounds, in which dual activation of both terminal alkynes and carbonyls was found in the presence of an indium(III) catalyst.[8a] Moreover, catalytic asymmetric alkynylation of aldehydes could be readily achieved using an In(III)/BINOL complex.[8b,c]

In comparison to the alkynylation of aldehydes and ketones,[9] addition of acetylide to imines and imine derivatives is far fewer reported due to the relatively poor electrophilicity of the azomethine carbon. Although there have been several methods of activation of C=N bond by Lewis acid promotion[10] for the preparation of propargyl amines that can serve as important synthetic building blocks like the corresponding propargylic alcohols, direct alkynylation of imino substrates with terminal alkynes remains an important and challenging topic. To our knowledge, indium salt-mediated alkynylation of nitrones has not been described before. Herein, we wish to present an efficient and practical process for synthesis of *N*-hydroxy-propargyl amines by $InBr_3$-catalyzed direct alkyne addition to nitrones under mild conditions.

Our studies were initiated by screening various imines and imine derivatives in the presence of indium(III) salt and tertiary amine such as *i*-Pr_2NEt which are similar to Shibasaki's conditions.[8a] However, unlike the catalytic alkynylation of carbonyl compounds, most reactions did not lead to the desired product except using nitrone as substrate. Encouraged by this finding, we then selected the reaction of *iso*-butyl nitrone **1a** and phenylacetylene for model studies. As shown in Table 1, $InBr_3$ was more reactive than $In(OTf)_3$ (entry 1 vs entry 3), and 15 mol % of catalyst was found to be suitable (entries 3–5). In addition, reducing the amount of phenylacetylene from 2 equiv to 1.5 equiv did not influence the yield (entries 4 and 6). These results demonstrated that treatment of nitrone and terminal alkyne with 15 mol % of $InBr_3$ and 20 mol % of *i*-Pr_2NEt at room temperature could afford propargylic *N*-hydroxylamine adducts in high yields. It is worth noting that, during these early investigation, we observed the formation of cyclization product 2,3-dihydroisoxazole[11] in toluene with $In(OTf)_3$ as catalyst (entry 2).

With optimal reaction conditions being identified, we then decided to investigate the scope of the method by evaluating this direct alkynylation of various nitrones with terminal alkynes. To our delight, the reaction seems to be general, as shown in Table 2, most nitrones derived from aliphatic aldehydes could react with phenylacetylene successfully to produce propargylic *N*-hydroxyamines in good to excellent yields. Linear (entries 2–5), α-branched (entries 1, 6–9), and β-branched (entry 10) aliphatic nit-

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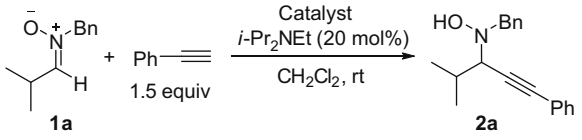
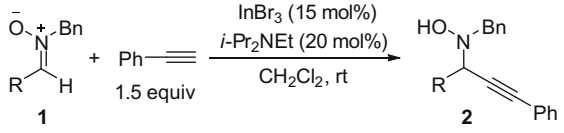
Table 1
Screening and optimization of the reaction conditions[a]



Entry	Catalyst	Mol %	Alkyne (equiv)	Solvent	Yield[b] (%)
1	$In(OTf)_3$	10	2	CH_2Cl_2	10
2	$In(OTf)_3$	10	2	Toluene	11[c]
3	$InBr_3$	10	2	CH_2Cl_2	40
4	$InBr_3$	15	2	CH_2Cl_2	84
5	$InBr_3$	20	2	CH_2Cl_2	86
6	$InBr_3$	15	1.5	CH_2Cl_2	89
7	$InBr_3$	15	1.2	CH_2Cl_2	69

[a] The reaction was performed with 0.2 mmol of nitrone in 1 mL of dry solvent at rt.
[b] Isolated yield.
[c] Isolated yield of cyclization product.

Table 2
$InBr_3$-catalyzed alkynylation of aliphatic nitrones[a]



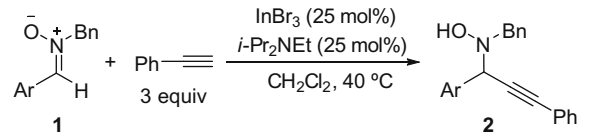
Entry	1: R	Time (h)	2	Yield[b] (%)
1	**1a** i-C_3H_7	1	**2a**	89
2	**1b** n-C_3H_7	1	**2b**	87
3	**1c** n-C_4H_9	4	**2c**	97
4	**1d** n-C_6H_{13}	1	**2d**	92
5	**1e** C_2H_5	1	**2e**	91
6	**1f** $C_2H_5(CH_3)CH$	1.5	**2f**	95
7	**1g** $(C_2H_5)_2CH$	1.5	**2g**	95
8	**1h** i-C_4H_9	1	**2h**	84
9	**1i** c-C_6H_{11}	1	**2i**	92
10[c]	**1j** c-C_3H_5	20	**2j**	89

[a] The reaction was carried out with $InBr_3$ (0.03 mmol), i-Pr_2NEt (0.04 mmol), phenylacetylene (0.3 mmol), and nitrone (0.2 mmol) in dry CH_2Cl_2 (1 mL) at rt. See Ref. 12 for experimental procedure.
[b] Isolated yield.
[c] Stirred at 40 °C.

rones are all suitable substrates. It should be noted that, performing the same reaction with cyclopropyl nitrone **1j** under optimal conditions gave a more sluggish conversion and the nitrone could not be consumed completely. Eventually, we were pleased to find that the reaction was dramatically improved when elevating temperature to 40 °C (entry 10). Moreover, it was found that the reaction could also be accomplished well in high yield using the base Et_3N instead of i-Pr_2NEt.

Next our attention was devoted to the addition of terminal alkyne to nitrones derived from aromatic aldehydes. Not surprisingly, the reactions proceeded not so well as described above because of the lower reactivity of aromatic nitrones in contrast to the corresponding aliphatic ones.[2a] With phenyl nitrone **1k** as model substrate, the optimal reaction conditions were reinvestigated. It was found that a moderate yield could be reached by increasing the loading of the catalyst $InBr_3$ and terminal acetylene to 25 mol % and 3 equiv, respectively. Slight warming (40 °C) was also effective for the smooth reaction. Finally, combining 25 mol % of $InBr_3$ and 25 mol % of i-Pr_2NEt into a solution of phenylacetylene (3 equiv) and nitrone (1 equiv) in CH_2Cl_2 at 40 °C gave the desired adducts in good yield (74%) after 24 h (Table 3, entry 1).

Table 3
$InBr_3$-catalyzed alkynylation of aromatic nitrones[a]



Entry	1: Ar	Time (h)	2	Yield[b] (%)
1	**1k** C6H5	24	**2k**	74
2	**1l** o-MeC6H4	24	**2l**	80
3	**1m** p-MeOC6H4	24	**2m**	74
4	**1n** o-BrC6H4	24	**2n**	81
5	**1o** m-ClC6H4	24	**2o**	66
6	**1p** p-BrC6H4	24	**2p**	68
7	**1q** p-FC6H4	24	**2q**	74
8	**1r** 2-Furyl	24	**2r**	40
9	**1s** m-$NO_2C_6H_4$	24	**2s**	55
10	**1t** p-$NO_2C_6H_4$	24	**2t**	50

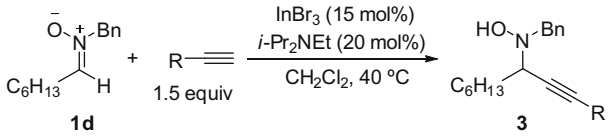
[a] The reaction was carried out with $InBr_3$ (0.05 mmol), i-Pr_2NEt (0.05 mmol), phenylacetylene (0.6 mmol), and nitrone (0.2 mmol) in dry CH_2Cl_2 (1 mL) at 40 °C for 24 h. See Ref. 12 for experimental procedure.
[b] Isolated yield.

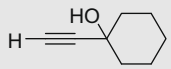
Other aromatic nitrones bearing various electron-withdrawing or electron-donating substituents could also be successfully applied for alkynylation, the results are summarized in Table 3.

Additionally, as exemplified in Table 4, with heptyl nitrone **1d**, a further study of the reaction generality and scope was carried out using some representative terminal acetylenes. In most cases, the corresponding propargylic *N*-hydroxyamines **3a–f** were obtained in good yields. From the results we also observed that some functional groups such as cyano and hydroxyl groups could be tolerated during the reaction.

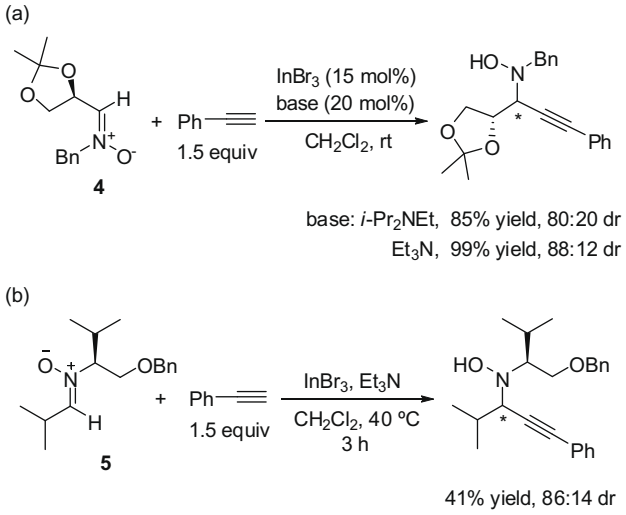
The established method was also applied to synthesize optically active propargylic *N*-hydroxyamines[2a,d,13] that can serve as highly valuable building blocks for asymmetric organic synthesis. Reac-

Table 4
$InBr_3$-catalyzed alkynylation of heptyl nitrone[a]



Entry	Alkyne	Time (h)	3	Yield[b] (%)
1	H—≡—$SiMe_3$	3	**3a**	73
2	H—≡—$(CH_2)_3CH_3$	3	**3b**	84
3	H—≡—$(CH_2)_3CN$	1	**3c**	82
4	H—≡—^tBu	1	**3d**	81
5	H—≡—$(CH_2)_3OH$	48	**3e**	44
6		1	**3f**	75

[a] The reaction was carried out with $InBr_3$ (0.03 mmol), i-Pr_2NEt (0.04 mmol), phenylacetylene (0.3 mmol), and nitrone (0.2 mmol) in dry CH_2Cl_2 (1 mL) at 40 °C.
[b] Isolated yield.

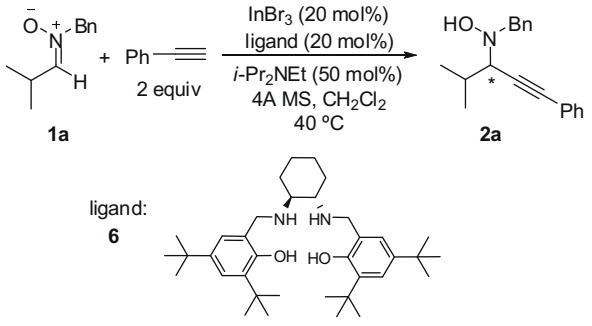


Scheme 1. $InBr_3$-induced diastereoselective alkynylation of chiral nitrones.

tion of phenylacetylene and chiral *N*-benzyl-D-glyceraldehyde-derived nitrone **4** was firstly examined. As summarized in Scheme 1a, good diastereoselectivities (up to 88:12) as well as excellent yields (99%) were observed, especially when simply switching the base from *i*-Pr_2NEt to Et_3N. While lowering the reaction temperature led to no desired improvement on the diastereoselectivity. It is worth noting that, when compared to the $Zn(OTf)_2$-involved procedure developed by Carreira,[2d] less catalyst loading and reaction time (2 h) were required. Moreover, the reaction could be run under air atmosphere, rendering unnecessary the need for N_2 protection.

On the other hand, we investigated another type of chiral nitrone (**5**)[14] with a (*R*)-valinol-derived chiral auxiliary, transferring the chiral center from α-carbon to the carbon close to nitrogen atom (Scheme 1b). Surprisingly, the alkynylation did not proceed well under the above-optimized conditions even at 40 °C, only gave a trace formation of product. When both the catalyst and base loading of $InBr_3$ and Et_3N were increased to 25 mol %, the yield of reaction was promoted to 41%, and a similar good diastereoselectivity (86:14) as using D-glyceraldehyde derived nitrone **4** was observed. By changing the solvent further to toluene or THF did not help to improve the result.

In an attempt to extend our exploration of asymmetric alkynylation further, we then envisioned the possibility of enantioselective addition of alkynes to nitrones by a chiral indium(III) complex. Catalytic asymmetric addition of alkynylzinc reagents to nitrones has been recently reported,[2a,13a] but direct alkyne addition using a chiral indium catalyst remains unrealized. Accordingly, the reaction between *iso*-butyl nitrone **1a** and



Scheme 2. Catalytic enantioselective alkynylation of nitrone.

phenylacetylene was firstly studied with Shibasaki's In(III)/BINOL system.[8b] To our disappointment, the enantioselectivity was low.[15] Several other chiral compounds such as BINOL derivatives, amino alcohols, diamines, and salen derivatives were also examined as ligands. At this stage, salan **6** was determined to be the best; product **2a** was obtained with 47% ee though the yield was still low (23%) (Scheme 2).

In summary, we have developed an indium(III)-catalyzed direct and efficient alkynylation of nitrones with terminal alkynes. The reactions could be accomplished with ease in the presence of $InBr_3$ and simple tertiary amine under mild conditions to afford a variety of synthetically very useful *N*-hydroxy-propargyl amine derivatives in good yields. By applying this method to chiral nitrones, good diastereoselectivities were observed and optically active propargylic *N*-hydroxyamines could be available. In addition, the first example of chiral indium(III) complex-catalyzed enantioselective alkynyl addition to nitrone was described. Further studies on improving the catalytic asymmetric addition are in progress.

Acknowledgments

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12. *Typical procedure*: Under nitrogen atmosphere, $InBr_3$ (0.03–0.05 mmol) was added to a dry flask, then CH_2Cl_2 (0.5 mL), phenylacetylene (0.3 mmol), and *i*-Pr_2NEt (0.04–0.05 mmol) were successively added. After stirring for 5 min at room temperature, nitrone (0.2 mmol) in CH_2Cl_2 (0.5 mL) was added. Then the reaction mixture was stirred at room temperature or at 40 °C until the nitrone was consumed. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The combined organic phase was dried

over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel flash chromatography to afford the corresponding propargylic *N*-hydroxyamine. Spectroscopic data for selected products: Compound **2c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, J = 7.2 Hz, 3H), 1.30–1.41 (m, 2H), 1.43–1.53 (m, 2H), 1.80–1.89 (m, 2H), 3.74 (t, J = 7.2 Hz, 1H), 3.94 and 4.16 (2d, AB, J_{AB} = 13.2 Hz, 2H), 4.95 (br s, 1H, OH), 7.25–7.50 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.4, 28.6, 33.0, 86.1, 86.9, 122.9, 127.4, 128.1, 128.2, 128.3, 129.6, 131.8, 137.1; MS (ESI) *m/z*: 294.1 ($M+H^+$). Compound **2h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, J = 5.7 Hz, 6H), 1.73 (t, J = 7.2 Hz, 2H), 1.89–1.96 (m, 1H), 3.83 (t, J = 7.2 Hz, 1H), 3.95 and 4.10 (2d, AB, J_{AB} = 12.9 Hz, 2H), 5.37 (s, 1H, OH), 7.24–7.51 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 22.8, 25.1, 42.0, 86.0, 86.9, 122.9, 127.4, 128.1, 128.2, 128.3, 129.6, 131.8, 137.1; MS (ESI) *m/z*: 294.0 ($M+H^+$). Compound **2l**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.03 and 4.12 (2d, AB, J_{AB} = 12.9 Hz, 2H), 4.80 (s, 1H), 5.18 (s, 1H), 7.18–7.84 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 84.8, 88.3, 122.8, 125.7, 127.5, 128.1, 128.2, 128.3, 129.6, 129.8, 130.5, 131.9, 135.6, 136.9; MS (ESI) *m/z*: 350.0 ($M+Na^+$). Compound **2p**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.03 and 4.11 (2d, AB, J_{AB} = 12.9 Hz, 2H), 4.91 (s, 1H), 4.94 (s, 1H), 7.26–7.58 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.7, 89.1, 122.0, 122.4, 127.6, 128.3, 128.4, 128.6, 129.5, 130.5, 131.4, 131.9, 136.7, 137.0; MS (ESI) *m/z*: 392.0 ($M+H^+$). Compound **3c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.0 Hz, 3H), 1.22–1.33 (m, 6H), 1.35–1.44 (m, 2H), 1.54–1.76 (m, 2H), 1.87–1.99 (m, 2H), 2.49 (t, J = 6.6 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 3.47 (t, J = 6.6 Hz, 1H), 3.81 and 4.00 (2d, AB, J_{AB} = 12.9 Hz, 2H), 5.22 (s, 1H, OH), 7.26–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 16.1, 17.9, 22.5, 24.7, 26.3, 28.9, 31.7, 33.4, 78.9, 83.8, 119.2, 127.4, 128.3, 129.5,137.1; MS (ESI) *m/z*: 313.2 ($M+H^+$).

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15. Both $InBr_3$ and $In(OTf)_3$ were examined with BINOL, only around 20% ee was observed though the yields were good (~90%).