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An Indium(III)-Catalyzed Synthesis of 4,4-Dichloro-1-aryl-*N*-alkyl-1-yn-3-amines *via* an Intermolecular C(sp^2)–C(sp) Bond Formation

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Abstract: This paper demonstrates an indium(III) triflate-catalyzed reaction of electron-deficient α,α-dichloroaldimines with terminal alkynes leading to a rapid and selective access to highly functionalized propargylic amines in good to excellent yields. The dichloromethylene moiety of the aldimine acts as an activating group to accomplish this transformation under very mild conditions.

Keywords: A^2-coupling; C–H activation; α-chloro imines; indium(III) catalysis; propargylic amines

Propargylic amines are versatile building blocks for a variety of fundamental organic transformations[1] and have proved to be important precursors for the synthesis of therapeutic drug molecules and complex natural products.[2] Additionally, these substructures have attracted substantial interest in medicinal chemistry due to their remarkable physiological activities.[3] Moreover, a broad range of propargylic amines are active towards the fragmentation of nucleosomal DNA, activation of caspase and the apoptotic cascade preventing collapse of mitochondrial membrane potential.[4] Propargylic amines such as rasagiline and selegiline are active in preventing cell death and are admired alternatives to L-DOPA for the treatment of Parkinson's disease, respectively.[5] Apart from their huge application in medicinal chemistry and pharmaceuticals[6] various propargylic amines are valuable as herbicides and fungicides.[7]

Herein, we disclose a new, efficient and convenient $In(OTf)_3$-catalyzed reaction between α,α-dichloroaldimines and terminal alkynes for the synthesis of a series of highly substituted dichloro- and trichloropropargylic amines in high to excellent yields.

In the past few years, a great deal of research has been devoted towards the development of an efficient and mild synthesis of propargylic amines.[8] Among the available methods, most of the procedures rely on the addition of stoichiometric quantities of organometallic reagents to imines. An efficient method using terminal alkynes thus remains limited. To achieve this purpose, various metal salts including Cu(I), B(III), Ag(I), Zn(II), Zr, Fe(III), Ni(II), Au(I), Au(III), In(III) and Ir complexes have been employed as catalysts in the reaction between imines or *in situ* generated imines and the corresponding terminal alkynes or organometallic reagents.[9] In view of the fact that the above-mentioned conventional methods are well applicable for the reaction of a series of imines with terminal alkynes, this synthetic strategy was applied for the transformation of α,α-dichloroaldimines to the corresponding propargylic amines using terminal alkynes as reactant. The availability of a convenient preparation of β,β-dichloropropargylic amines amines would allow one to further investigate the reactivity of these highly functionalized compounds.[10d] We have therefore screened the most efficient and common reaction conditions for the synthesis of propargylic amines (*vide infra*).[9a,b,k,m–o] Remarkably, these methods only led to very low conversions for the transformation of α,α-dichloroaldimines to the corresponding propargylic amines. More recently, our research group has reported a convenient synthetic route towards propargylic amines by the reaction of α,α-dichloroaldimines and potassium alkynyltrifluoroborates using a Lewis acid-mediated Mannich type reaction.[10] The fact that potassium alkynyltrifluoroborate must be prepared in a separate step by metalation of the corresponding alkyne with a highly reactive organometallic reagent (BuLi, EtMgBr, or LDA) anhydrously and under inert atmosphere at low temperature remains a disadvantage. Furthermore, subsequent borylation with $B(O\text{-}i\text{-}Pr)_3$ is an additional drawback. Therefore, we developed a new direct addition reaction of alkynes to functionalized imines. Due to the poor electrophilicity of the azomethine carbon,

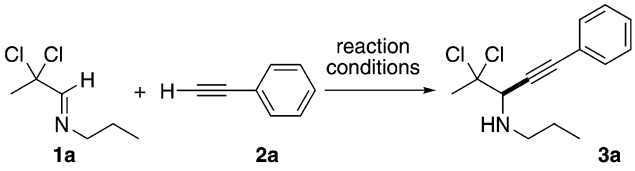
a Lewis acid activator like $In(OTf)_3$ was used, which also increases the acidity of the C(*sp*)–H atom by formation of a π-complex with the alkyne, thereby facilitating the formation of the active nucleophilic species. This catalytic alkynylation is similar to the dual activation by an indium(III) catalyst of soft nucleophiles, like terminal alkynes and hard electrophiles, like aldehydes.[11] In modern organic synthesis, the use of indium salts as catalysts has become of increasing interest due to their easy availability, low toxicity and high endurance with regard to functional groups.[12] Moreover it should be mentioned that indium is a cheaper metal then, for instance, silver which is also often used as a catalyst. Recently, In(III) species have been used as Lewis acids in several transformations.[13]

As a preliminary experiment, model substrates *N*-(2,2-dichloro-1-propylidene)amine (**1a**) and phenylacetylene (**2a**) were reacted in the presence of 5 mol% of CuBr in toluene as solvent at 60 °C for 18 h and 4 h, respectively, under argon according to a recent literature procedure.[9a,b,k,m–o] Unfortunately, it was observed that the reaction afforded a complex mixture and the desired product 4,4-dichloro-1-phenyl-*N*-propylpent-1-yn-3-amine (**3a**) could not be identified.

Inspired by the negative results from preliminary experiments, further studies were continued in order to find suitable reaction conditions to accomplish this transformation. Screening of the reaction conditions revealed that the corresponding product **3a** was isolated in 7% yield when the reaction was carried out using 25 mol% of CuBr in dichloromethane as solvent at 50 °C for 18 h (Table 1, entry 1). Interestingly, it was found that by replacing CuBr by $Cu(OTf)_2$ as catalyst, the corresponding product **3a** could be isolated in 44% yield (Table 1, entry 2) and performing the reaction at 100 °C for 6 h delivered the product **3a** in 11% yield (Table 1, entry 3). Moreover, $CuCl_2$ as catalyst was almost inactive for this transformation as the reaction produces **3a** only in 2% yield (Table 1, entry 4). Apart from copper sources as catalyst, $AuCl(PPh_3)$, In(III), Zn(II) and Fe(III) were also effective (Table 1, entries 5–14) and among the catalysts tried for this transformation $In(OTf)_3$ was the most effective and delivered the maximum isolated yield of the product **3a** (Table 1, entries 8–10). Notably, by replacing air by argon as reaction atmosphere no significant improvement in the yield of **3a** has been observed (Table 1, entry 10).

In view of the yields and the reaction conditions in Table 1, a maximum yield of 69% of product **3a** could be obtained when 0.5 mmol of **1a** was reacted with 0.5 mmol of **2a** in the presence of 25 mol% of $In(OTf)_3$ as catalyst and CH_2Cl_2 as solvent at 50 °C for 18–24 h in a sealed vial (Table 1, entry 9, for further optimization see the Supporting Information).

Table 1. Screening of the reaction conditions for the reaction between **1a** and **2a**.[a]



1a **2a** **3a**

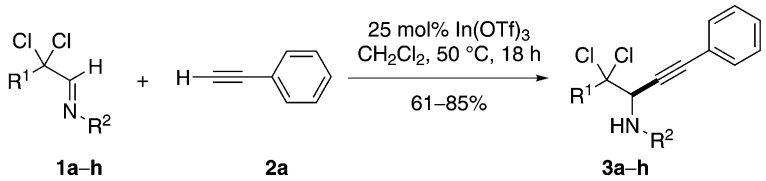
Entry	Catalyst/[mol%]	Solvent	*T*/*t* [°C/h]	Yield of **3a** [%]
1	CuBr/25	CH_2Cl_2	50/18	7[b]
2	$Cu(OTf)_2$/25	CH_2Cl_2	50/18	44[b]
3	$Cu(OTf)_2$/5	PhMe	100/6	11[b]
4	$CuCl_2$/25	CH_2Cl_2	50/18	2[b]
5	$AuCl(PPh_3)$/25	CH_2Cl_2	50/18	41[b]
6	$AuCl(PPh_3)$/100	CH_2Cl_2/HFIP[d]	r.t./18	61[c]
7	$AuCl(PPh_3)$/50	CH_2Cl_2/HFIP[d]	r.t./18	37[c]
8	**$In(OTf)_3$/50**	**CH_2Cl_2**	**r.t./18**	**71**[c]
9	**$In(OTf)_3$/25**	**CH_2Cl_2**	**50/24**	**69**[c]
10	**$In(OTf)_3$/25**	**CH_2Cl_2**	**50/24**	**70**[c,e]
11	$InCl_3$/25	CH_2Cl_2	50/18	43[b]
12	$ZnCl_2$/25	CH_2Cl_2	50/18	43[b]
13	$Zn(OTf)_2$/25	CH_2Cl_2	50/18	23[b]
14	$FeCl_3$/25	CH_2Cl_2	50/18	16[f]

[a] Unless otherwise indicated, all reactions were performed using 0.5 mmol **1a** and 0.5 mmol **2a** in a sealed vial under air.
[b] Yield without acid-base work-up.
[c] Yield after acid-base work-up.
[d] In 9:1 ratio.
[e] Reaction performed under argon.
[f] Predicted from ^{1}H NMR (without acid-base work-up), additionally an unidentified compound was observed in ^{1}H NMR.

These reaction conditions were considered as optimal and were used for further reactions. In general, these β,β-dichloroamines could be simply purified and obtained in excellent yield by acid-base extraction. Purification of these propargylic amines by means of flash chromatography on silica gel resulted in considerable loss of product and resulted in a very impure product.[10d]

Using the optimized conditions, the scope of the reaction was explored using a broad range of chlorinated imines **1a–h**. It was observed that a number of substituents on the imine, including methyl, ethyl, isopropyl, *tert*-butyl, allyl, benzyl and chloro groups were tolerated to achieve the corresponding products **3a–h** in 62–85% yields (Table 2, entries 1–8). In the case of *N*-benzylimine **1e** (Table 2, entry 5), isomerization of the C=N double bond to the *N*-benzylidene derivative was not considered as an alternative as the α′-alkynylated product was not observed.[14] On the other hand, the scope of arylacetylenes has also been studied. It

Table 2. $In(OTf)_3$-catalyzed reaction between **1a–h** and phenylacetylene (**2a**).[a]



1a–h **2a** **3a–h**

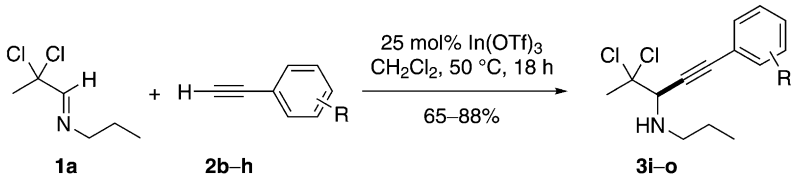
Entry	**1**	**3**	Yield of **3** [%]
1	**a**		75[b]
2	**b**		66;[b] 65[c]
3	**c**		85;[b] 83[c]
4	**d**		69;[b] 66[c]
5	**e**		73;[b] 72[c]
6	**f**		69;[b] 62[c]
7	**g**		66;[b] 61[c]
8	**h**		79;[b] 76[c]

[a] All reactions were performed using 0.5 mmol **1** and 0.5 mmol **2a** in a sealed vial under air.
[b] Yield without acid-base work-up.
[c] Yield after acid-base work-up.

revealed that a number of electron-donating substituents (methyl, ethyl, *tert*-butyl and methoxy) as well as electron-withdrawing substituents (chloro and fluoro) on the aromatic ring of the arylacetylenes **2b–h** were well tolerated to produce the corresponding products **3i–o** in 65–88% yields (Table 3, entries 1-7).

Moreover, the generality of this method has been verified by reacting **1a** with cyclohexylacetylene (**2i**), 1-hexyne (**2j**) and methyl propargyl ether (**2k**) (Scheme 1). Surprisingly, the developed alkynylation method is not only restricted to the use of arylacetylenes but is also applicable for alkylacetylenes and in

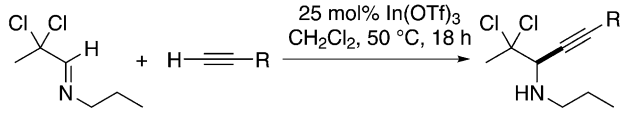
Table 3. $In(OTf)_3$-catalyzed reaction between **1a** and arylacetylenes **2b–h**.[a]



1a **2b–h** **3i–o**

Entry	R	3	Yield of 3 [%]
1	2-methyl; **2b**	**i**	74;[b] 67[c]
2	4-methyl; **2c**	**j**	88;[b] 79[c]
3	4-ethyl; **2d**	**k**	78;[b] 71[c]
4	4-*tert*-butyl; **2e**	**l**	70;[b] 65[c]
5	3-methoxy; **2f**	**m**	79;[b] 71[c]
6	4-chloro; **2g**	**n**	66[c]
7	4-fluoro-3-methyl; **2h**	**o**	85;[b] 72[c]

[a] All reactions were performed using 0.5 mmol **1a** and 0.5 mmol **2** in a sealed vial under air.
[b] Yield without acid-base work-up.
[c] Yield after acid-base work-up.



1a **2i–k** **3p–r**

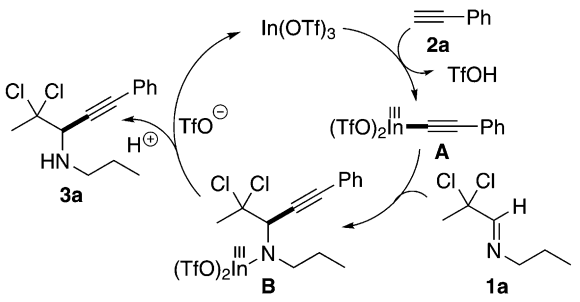
R = cyclohexyl; 81%[a] (83%[b])
R = *n*-butyl; 87%[a] (85%[b])
R = CH_2OMe; 61%[a]

[a] Yield without acid-base work-up,
[b] Yield after acid-base work-up

Scheme 1. $In(OTf)_3$-catalyzed reaction between **1a** and alkylacetylenes **2i–k**.

all cases the corresponding final products **3p–r** were isolated in good to excellent yields.

A possible mechanism for this In(III)-catalyzed alkynylation is proposed in Scheme 2. Most probably the first step is the insertion of In(III) into the acidic C(*sp*)–H bond of the terminal acetylene to deliver an active indium(III) acetylide **A**. This insertion is accompanied by the release of one molecule of triflic acid. Due to its high nucleophilic character an addition reaction of the organoindium across the C=N double bond of the imine occurs, which leads to the



Scheme 2. Plausible mechanism of the In(III)-catalyzed alkynylation of imines.

formation of the intermediate **B**. Finally, intermediate **B** is protonated by triflic acid leading to the propargylic amine **3a** and hereby regenerating the active In(III) triflate (Scheme 2).

Several experiments were performed to support the proposed mechanism. An experiment with **1a** and phenylacetylene-*d* (**2l**) in the presence of 25 mol% $In(OTf)_3$ as a catalyst in CH_2Cl_2 as solvent at 50 °C revealed that the corresponding product **3a** can be isolated in 66% yield. It is noteworthy to mention that there is no incorporation of deuterium in the final product **3a** (Figure 1). Further support for the proposed mechanism was found by performing the alkynylation reaction in the presence of 2 equivalents of triethylamine as an additive. Product **3a** was isolated in 32% yield. This lower yield can be explained by assuming the neutralization of triflic acid by triethylamine, thus preventing the efficient regeneration of the $In(OTf)_3$ catalyst from intermediate **B**.[15] On the other hand, the addition of an extra equivalent of triflic acid to the alkynylation reaction led to a similar yield of **3a** (63%) as that obtained in the absence of any additive (66%).

In summary, an efficient and operationally simple In(III)-catalyzed synthesis of 4,4-dichloro-1-aryl-*N*-alkyl-1-yn-3-amines is demonstrated. The reaction proceeds under very mild conditions, producing the corresponding final products in good to excellent yields in high purity. Notably, the traditional reaction conditions for alkynylation of imines were unable to accomplish this particular transformation.

Experimental Section

General Experimental Procedure (I) for the In(III)-Catalyzed Synthesis of 3

In an oven-dried 10-mL vial α,α-dichlorinated aldimines (0.5 mmol), acetylenes (0.5 mmol) and $In(OTf)_3$

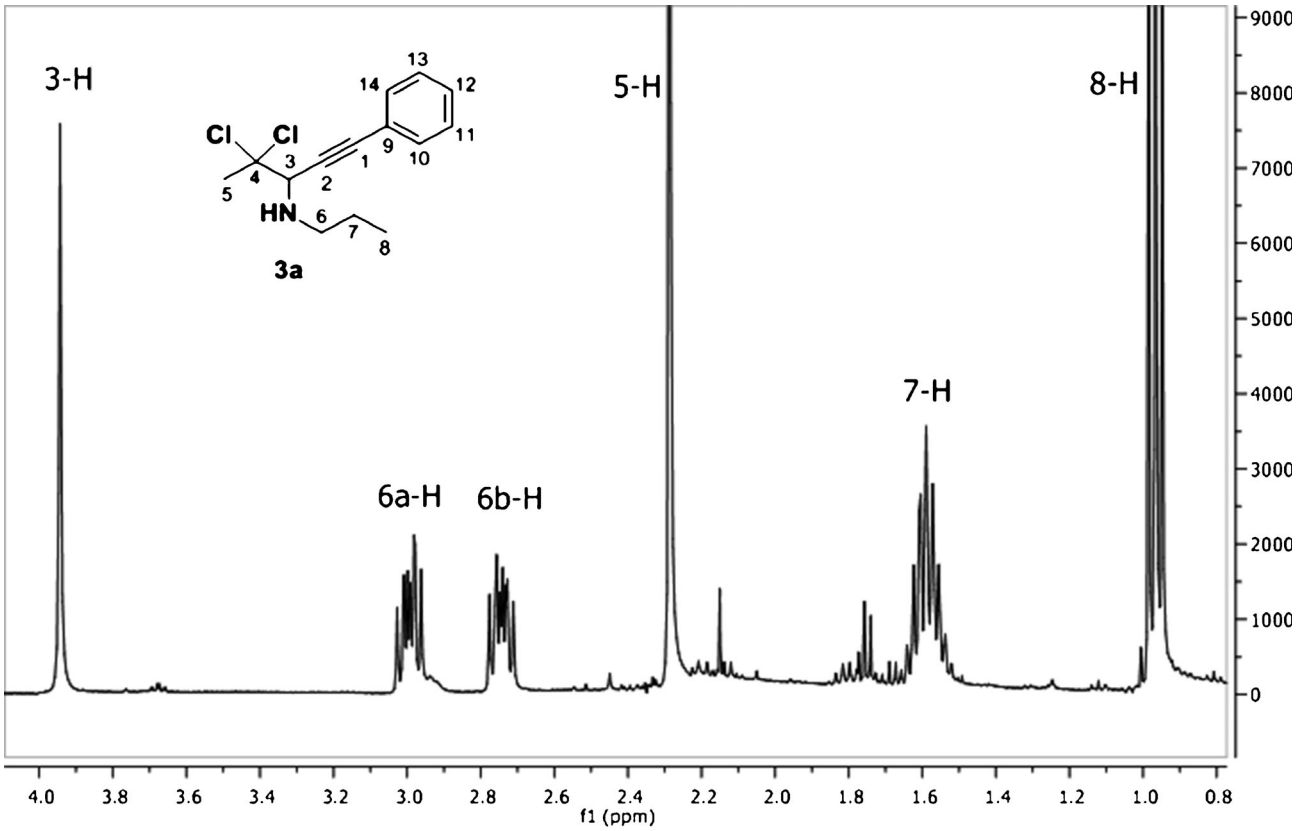


Figure 1. ^1H NMR spectrum of product **3a** from the experiment with phenylacetylene-*d* (**2l**).

(0.125 mmol, 70.3 mg) were added successively and the vial was sealed under air. Then, CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred at 50 °C for 18–24 h. Afterwards, the reaction mixture was extracted with 0.5 N NaOH (4 mL). The organic phase was dried using $MgSO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was then subjected to an acid-base extraction: 1 N HCl (4 mL) and CH_2Cl_2 (2 mL) were added and stirred for 1 h at room temperature. The aqueous phase was isolated and washed with diethyl ether (4 mL–4 mL–2 mL) and the combined organic phases were once more extracted with 2 N HCl (4 mL–2 mL–1 mL). Then, 3 N NaOH (~7 mL) was added to the aqueous phase until the pH was slightly basic and the resulting solution was extracted with CH_2Cl_2 (10 mL–10 mL–5 mL). The CH_2Cl_2 fractions were combined, dried using $MgSO_4$ and concentrated under vacuum to afford the corresponding 4,4-dichloro-1-aryl-*N*-alkyl-1-yn-3-amine **3a–r** as yellow oils.

General Experimental Procedure (II) for the In(III)-Catalyzed Synthesis of 3

In an oven-dried 10-mL vial α,α-dichlorinated aldimines (0.5 mmol) **1a**–**h**, acetylenes **2a**–**h** (0.5 mmol) and $In(OTf)_3$ (0.125 mmol, 70.3 mg) were added successively and the vial was sealed under air. CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred at 50 °C for 18–24 h. Afterwards, the reaction mixture was diluted with 10 mL CH_2Cl_2 and washed with 0.5 N NaOH (10 mL). The CH_2Cl_2 fractions were combined, dried using $MgSO_4$ and concentrated under vacuum to afford the corresponding 4,4-dichloro-1- aryl-*N*-alkyl-1-yn-3-amines **3a–r** as yellow oils.

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