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Indium catalyzed tandem hydroamination/hydroalkylation of terminal alkynes†

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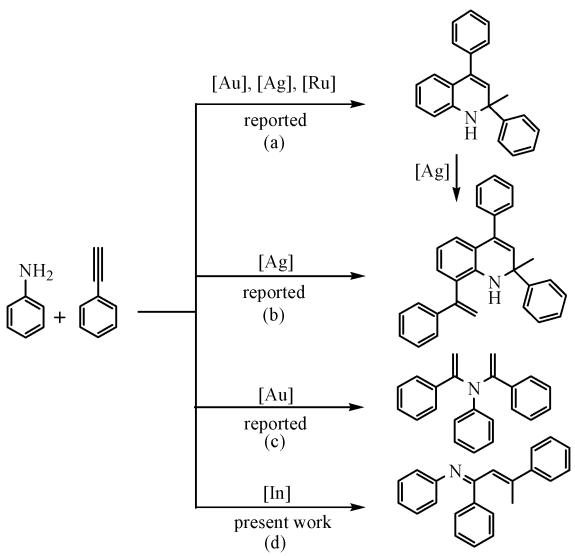
The first direct intermolecular hydroamination/hydroalkylation of terminal alkynes catalyzed by $In(OTf)_3$ under one-pot conditions leading to the formation of conjugated ketimines in good yields is described.

In recent years, considerable effort has been devoted to develop methodologies which reduce multi-step transformations into one-step tandem processes.[1] In this regard, the use of multi-functional catalysts, which promote sequential reaction steps without additional requirement of additives and/or co-catalysts, provides an effective way while taking care of two most basic challenges faced by a synthetic chemist, *i.e.* atom-economy and cost-reduction.[2] The addition of N–H and C–H bonds across C–C π systems, also known as hydroamination and hydroalkylation, is one of the most interesting and intriguing subjects in synthetic organic chemistry, as they provide an attractive route for construction of a plethora of versatile building blocks. A variety of efficient catalytic systems have been developed for hydroamination of alkynes.[3] However, hydroalkylation of alkynes is a relatively less studied area with most of the processes following an intramolecular pathway.[4] Although the addition reaction of amines across the π system of terminal alkynes is studied in detail with various combinations of metal catalysts, interest in this area has been rejuvenated over the last half decade with some very interesting results (Scheme 1). Reaction of aniline with excess of alkyne has been reported to produce dihydroquinazoline over gold, silver and ruthenium catalysis (paths a and b, Scheme 1), where the reaction sequence involves hydroamination followed by cyclization *via* aromatic C–H activation.[5] In a recent report, Corma and his co-workers have reported a gold(I) catalyzed intermolecular double-hydroamination of the anilines with terminal alkynes to obtain aryl bisenamines as unexpected products[6] (path c, Scheme 1). Despite the numerous protocols for hydroamination and hydroalkylation of terminal alkynes available in the literature, to the best of our knowledge there is no report of any catalytic process where both the reaction steps occur concomitantly under the same reaction conditions. Previously, we have demonstrated that indium effectively activates terminal alkynes for cross coupling reaction as well as for nucleophilic addition.[7] We report herein the first example of indium catalyzed tandem hydroamination and hydroalkylation of terminal alkynes with arylamines to generate α,β-unsaturated ketimines (path d, Scheme 1). Conjugated imines are versatile building blocks for construction of nitrogen heterocycles.[8] Heterocycles such as pyrroles,[9a] pyrazoles,[9b] pyrimidines,[9c] pyridines,[9d] indolizines,[9e] quinolines[9f] and even α-amino acids[9g] and medium-sized carbocycles[9h] can be obtained by functionalization of these interesting subunits. As such, rapid and efficient approaches to the conjugated ketimines, especially under one-pot conditions[10] are highly sought after because of their immense synthetic potential.

In the present study, we show that indium effectively acts as a double catalyst for both hydroamination and hydroalkylation of terminal alkynes when reacted with arylamines. Preliminary studies were directed to investigate the catalytic action of indium trifluoromethanesulfonate on the hydroamination reaction of terminal alkynes with arylamines. Initially, reaction of *p*-toluidine with 1.1 equivalents of phenylacetylene was carried out. Formation of the desired imine by Markovnikov addition of



Scheme 1 Reaction of aniline with phenylacetylene under various catalytic conditions.

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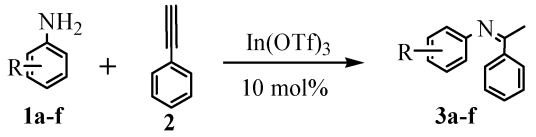
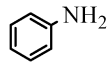
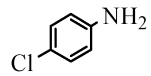
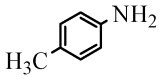
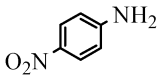
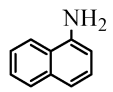
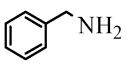
† Electronic supplementary information (ESI) available: Detailed experimental procedure, compound characterization data and NMR spectra. CCDC 828855. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc13486h

Table 1 Hydroamination of phenylacetylene with different amines[a]



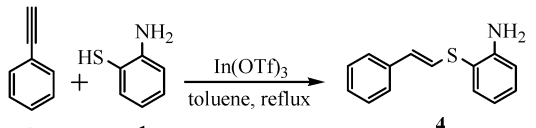
1a-f 2 3a-f

Entry	Amine	Product	%Yield[b]
1		**3a**	90
2		**3b**	92
3		**3c**	94
4		**3d**	88
5		**3e**	90
6		**3f**	2

[a] Reaction conditions: amine (5 mmol), phenylacetylene (5.5 mmol) and $In(OTf)_3$ (0.5 mmol) were refluxed in toluene (10 mL) for 3 h. [b] Yield of isolated products.

the amine to the alkyne in excellent yield was observed when the reactants were refluxed in toluene for 3 h by employing 10 mol% of $In(OTf)_3$ as a catalyst. The feasibility of the reaction was studied by employing various arylamines and benzylamine and the results are summarised in Table 1. It was observed that all arylamines underwent the reaction smoothly and gave excellent yields (entries 1–5, Table 1) whereas benzylamine was quite reluctant to participate in the reaction and gave negligible yield (entry 6, Table 1). The recyclability of the catalyst was also investigated and it was found that the catalyst retained its activity up to 3 catalytic cycles and showed minor loss in activity over 4th and 5th cycles (see Table S1, ESI†). However, when a competing thiol moiety is present in the arylamine, exclusive hydrothiolation occurred *via* anti-Markovnikov addition with no hydroamination product. So, when 2-aminothiophenol was reacted with phenylacetylene in refluxing toluene by employing 10 mol% $In(OTf)_3$ as a catalyst, 2-(styrylthio)aniline was obtained as the only product (Scheme 2).

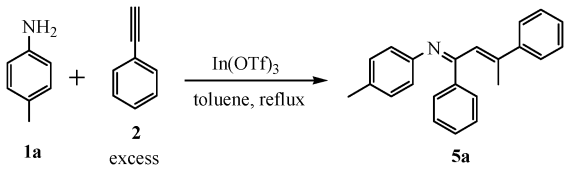
Very recently, we have reported that phenylacetylene undergoes indium mediated 1,2-addition with the imine double bond in the presence of a co-catalyst.[7c] This result motivated us to study the



2 1g 4

Scheme 2 Anti-Markovnikov hydrothiolation of phenylacetylene.

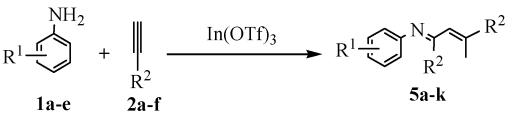
reaction of arylamine with excess of phenylacetylene. Accordingly, we carried out a reaction of *p*-toluidine with excess of phenylacetylene under identical conditions. Quite interestingly, though, we obtained a conjugated imine *N*-(1,3-diphenylbut-2-enylidene)-4-methylaniline **5a** as the unexpected product (Scheme 3). We became excited to observe this unprecedented catalytic activity of indium and set out to study the reaction in detail. We began by examining the reaction of *p*-toluidine with phenylacetylene in the presence of a catalytic amount of $In(OTf)_3$. Optimisation of the reaction conditions revealed that 10 mol% of the catalyst and three equivalents of the alkyne were necessary to get the best results (see Table S2, ESI†). Using the optimised conditions, the



1a 2 excess 5a

Scheme 3 Reaction of *p*-toluidine with phenylacetylene.

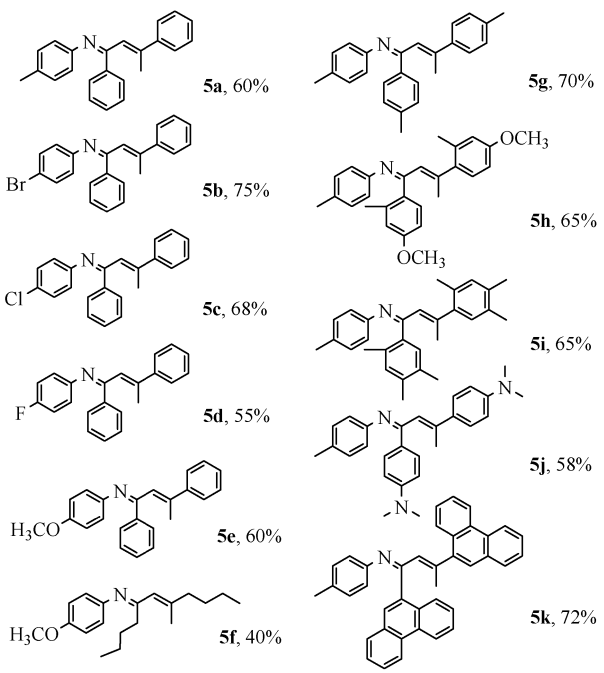
Table 2 Substrate scope for tandem hydroamination/hydroalkylation of terminal alkynes[a]



1a-e 2a-f 5a-k

R^1=**1a**:4-Me- **1d**: 4-F
1b:4-Br- **1e**: 4-OMe-
1c:4-Cl-

R^2=**2a**: C_6H_5- **2e**: 2,4,5-Me-C_6H_3-
2b: 4-Me-C_6H_4- **2f**: 9-phenanthrenyl
2c: 2-Me-4-OMe-C_6H_3- **2g**: n-butyl
2d: 4-NMe_2-C_6H_4-



[a] Reaction conditions: amine (5 mmol), phenylacetylene (15 mmol) and $In(OTf)_3$ (0.5 mmol) were refluxed in toluene (10 mL) for 18 h. %Yield refers to yield of isolated products.

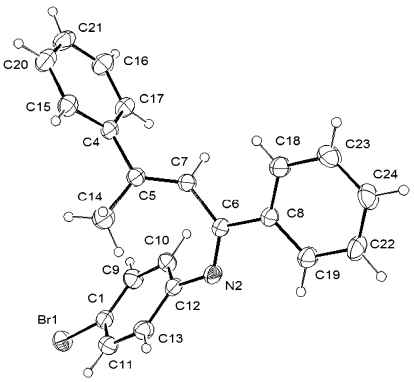
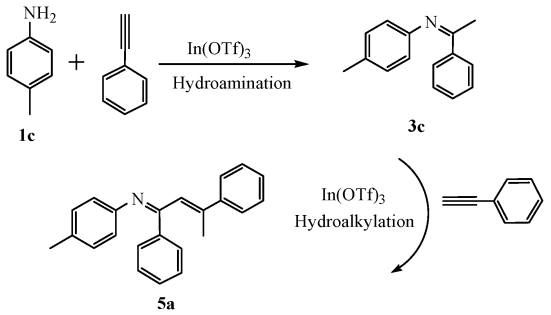


Fig. 1 Ortep diagram of compound **5b** drawn with 30% probability ellipsoid.

scope of the reaction was then investigated with a number of different arylamines as well as terminal alkynes and the results obtained are summarised in Table 2. Reaction of phenylacetylene with various arylamines afforded the conjugated ketimines in good yields (entries 5a–e, Table 2). We next examined the feasibility of the reaction by employing various aromatic alkynes having mono-, di- and tri-substituents and were pleased to find that smooth reaction occurred with comparable yields (entries 5g–k, Table 2). Aliphatic alkyne was also found to undergo the transformation, albeit with a lower yield (entry 5f, Table 2). However, some uncharacterised compounds were detected in all cases. All the products obtained were characterized by IR, NMR and mass spectrometry. Additionally, the structure of compound **5b** was confirmed by X-ray single crystal analysis (Fig. 1). However, an attempt to recover and reuse the catalyst failed, probably because of the formation of the uncharacterized products.

Although mechanistic studies are not performed, the formation of the conjugated ketimine product can be rationalised by an initial hydroamination of the alkyne followed by a second hydroalkylation step as shown in Scheme 4. To confirm the role of indium in the second hydroalkylation step of the reaction, we further reacted phenylacetylene with pre-formed imine **3c** generated from hydroamination of phenylacetylene with *p*-toluidine. Reaction of **3c** with two equivalents of phenylacetylene in the presence of 10 mol% of $In(OTf)_3$ under refluxing toluene led to the formation of product **5a** with minor improvement in yield as compared to the three component reaction. When the reaction is performed in the absence of the indium catalyst, no conversion of the reactants to the desired product was detected. This shows that indium is essential for the second hydroalkylation step to take place and the reaction follows an intermolecular pathway.

In summary, we have developed the first protocol for direct intermolecular hydroamination/hydroalkylation of terminal alkynes under one-pot conditions. $In(OTf)_3$ is shown to effectively act as a double catalyst for sequential hydroamination and hydroalkylation of terminal alkynes in the absence of any other additive and/or co-catalyst. A range of arylamines and alkynes were studied and good yields of the products were obtained. This methodology offers a new approach for the synthesis of conjugated ketimines from simple starting materials with excellent atom-economy.



Scheme 4 Sequential hydroamination/hydroalkylation of phenylacetylene.

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