Indium(III)-Catalyzed Tandem Hydroamination–Hydroarylation of Naphthylamines with Phenylacetylenes

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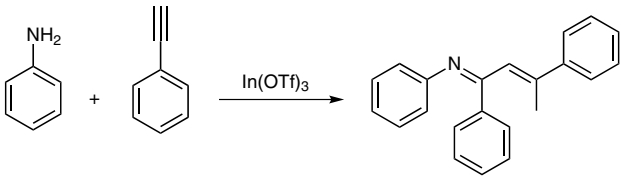
Abstract: A one-pot, three-component method for the synthesis of benzo-fused quinolines has been developed by tandem reaction between phenylacetylenes and naphthylamines. The first step of the reaction is hydroamination of the alkyne followed by a hydroarylation reaction to form the quinolines. Indium(III) trifluoromethanesulfonate was shown to be an efficient catalyst for the transformations, and the reaction proceeded in the absence of any other co-catalyst or additive to give the corresponding quinolines in good to excellent yields.

Key words: indium, alkynes, hydroamination, hydroarylation, domino reactions

In recent years, tandem processes for the construction of complex molecules by employing simple starting materials has emerged as an attractive alternative to conventional synthesis.[1] The popularity of tandem processes[2] over traditional multi-step procedures can be attributed to the significant reduction in cost, time, and waste generation as well as enhancement in the atom economy of the reaction, which is in accordance with the 'green chemistry' protocol.[3] In this regard, exploitation of suitable catalyst systems for the promotion of sequential reaction steps under one-pot conditions, especially in the absence of any other co-catalyst or additives, is an interesting and intriguing option that needs to be explored further.[4]

Quinolines are one of the most important heterocyclic subunits because of their natural abundance and immense pharmacological potency.[5] This has resulted in the devotion of considerable effort towards the development of newer methodologies for their synthesis.[6] Although significant numbers of efficient protocols have been developed for assembling this important substructure, the design of new one-pot tandem processes[7] for the construction of complex annulated quinolines remains a challenging area.

Over the last decade, the chemistry of indium catalysis has contributed enormously to the field of organic synthesis because of the ability of indium(III) reagents to catalyze carbon–carbon bond-forming reactions. In this context, of particular interest is the indium(III)-mediated activation of π-electrons of alkynes for the generation of a diverse range of synthetically and biologically important compounds.[8] Although a large number of organic transformations have been reported to take place under indium catalysis,[9] relatively little effort has been directed toward the development of tandem processes under one-pot conditions. Previously, we have demonstrated that indium trifluoromethanesulfonate[10] can be employed as an efficient catalyst for the activation of terminal alkynes for various reactions such as coupling reactions, nucleophilic addition, and hydrothiolation reactions in the absence of any other additives or co-catalysts.[11] Moreover, indium triflate has also been shown to catalyze the tandem hydroamination–hydroalkylation reaction of terminal alkynes with anilines for the generation of α,β-unsaturated ketimines (Scheme 1).[12] This result encouraged us to study the reaction between terminal alkynes and naphthylamine under indium-catalyzed conditions. Interestingly, we observed that, in presence of indium(III) catalyst, unlike anilines, naphthylamine reacted with phenylacetylene through a tandem hydroamination–hydroarylation pathway to give quinoline derivatives.[13,14] This type of tandem hydroamination–hydroarylation reaction of aniline with arylalkynes is known to proceed under silver and gold catalysis; however, those processes require co-catalysts, additives, and an excess amount of the alkyne for the transformation to take place.[15]



Scheme 1

In this paper, we report our preliminary findings for an indium(III)-catalyzed tandem hydroamination–hydroarylation of phenylacetylenes with naphthylamines for the synthesis of fused quinolines (Scheme 2). Preliminary studies were carried out to investigate the reaction between 2-naphthylamine and phenylacetylene. When 2-naphthylamine (**1a**) was heated to reflux with an excess of phenylacetylene (**2a**) in toluene by employing indium(III) triflate as catalyst, a 1,2-dihydrobenzo[*f*]quinoline product was obtained.

The reaction was optimized by varying the type and amount of catalyst, the amount of alkyne, and the reaction time; the results are summarized in Table 1. It was ob-

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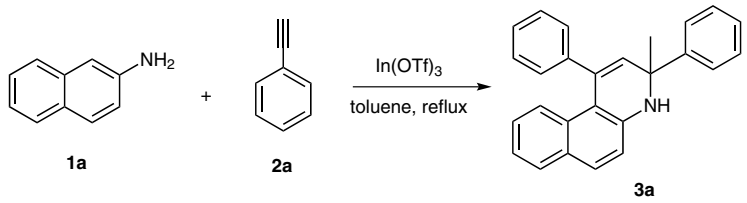


Scheme 2

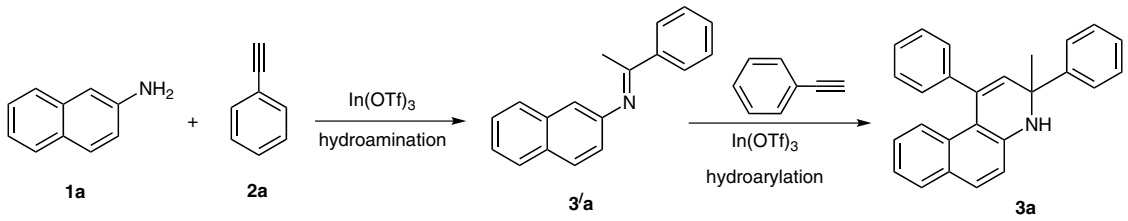
served that a maximum yield of 85% could be obtained when one equivalent of amine was reacted with four equivalents of alkyne in the presence of 10 mol% indium(III) triflate as catalyst (Table 1, entry 6). Other indium(III) catalysts such as indium(III) chloride or indium(III) bromide, or metallic indium did not give encouraging results (Table 1, entries 9–11). Similarly, other triflates such as zinc, scandium, or ytterbium triflates also gave poor yields compared with indium(III) triflate (Table 1, entries 12–14). The structure of **3a** was ascertained from spectroscopic data and elemental analysis. The ^{1}H NMR spectra of the compound showed the presence of the NH proton at δ = 4.72 ppm, a vinylic proton at δ = 5.82 ppm, and methyl protons at δ = 1.73 ppm as singlets. The IR spectra showed the presence of the NH group at 3374 cm^{-1}.[16]

The scope of the reaction was then investigated with a number of different alkynes and amines by employing the optimized conditions; the results are summarized in Table 2. It was observed that both 1-naphthylamine and 2-naphthylamine participated in the reaction to give fused benzo[*g*]quinoline and benzo[*f*]quinoline, respectively, with comparable yields. The reaction was also successful with alkynes with either electron-donating or electron-withdrawing groups (Table 2, entries 2–8). However, some uncharacterized compounds were detected in all cases, which could be separated by column chromatography. All the products obtained were characterized by IR, NMR spectroscopy and mass spectrometry.

Although mechanistic studies were not performed, the formation of the quinoline product may be rationalized by initial hydroamination of the alkyne followed by a second hydroarylation step (Scheme 3). In the first step, an electrophilic indium–alkyne complex is believed to form from indium(III) triflate and phenylacetylene, which then reacts with 2-naphthylamine to give a ketimine intermediate through Markovnikov addition. The next step may start with nucleophilic addition of an alkynylindium intermediate to the ketimine, followed by intramolecular hydroarylation to give quinoline **3a** as the final product. The significant difference in reactivity of naphthylamine as compared with anilines[12] toward the second molecule of phenylacetylene under identical reaction conditions results from the difference in reactivity of the hydroamination intermediate formed in the first step of the reaction. The presence of the highly electrophilic C-1 carbon atom in naphthylamine facilitates formation of the cyclic quinoline product through intramolecular hydroarylation. On the other hand, aniline does not have such favorable electrophilic centers adjacent to the imine double bond and, thus, is unable to undergo the cyclization step.

Table 1 Optimization Studies for the Synthesis of Quinoline Derivative **3a**

Entry	Catalyst	Cat. amount (mol%)	Alkyne (equiv)	Time (h)	Yield (%)
1	$In(OTf)_3$	0.5	10	15	trace
2	$In(OTf)_3$	5	10	10	25
3	$In(OTf)_3$	10	10	10	85
4	$In(OTf)_3$	20	10	10	82
5	$In(OTf)_3$	10	7	10	85
6	$In(OTf)_3$	10	4	10	85
7	$In(OTf)_3$	10	3	10	60
8	$In(OTf)_3$	10	2	10	20
9	$InCl_3$	10	4	15	55
10	$InBr_3$	10	4	15	55
11	In	10	4	18	10
12	$Zn(OTf)_2$	10	4	20	trace
13	$Sc(OTf)_3$	10	4	15	50
14	$Yb(OTf)_3$	10	4	15	50



Scheme 3

Table 2 Substrate Scope[a]

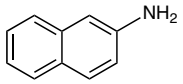
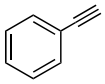
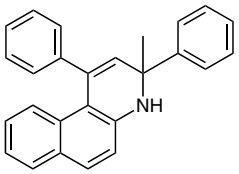
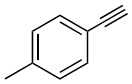
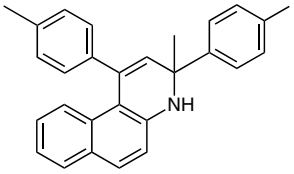
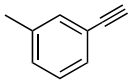
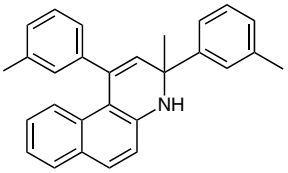
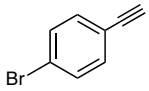
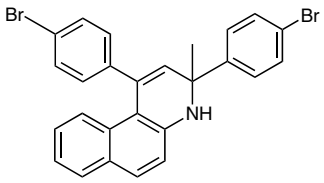
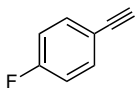
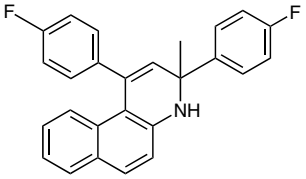
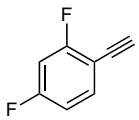
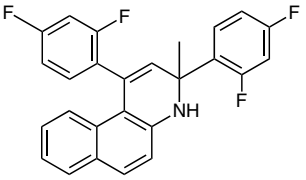
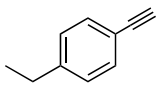
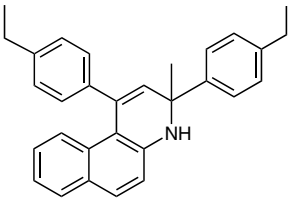
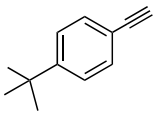
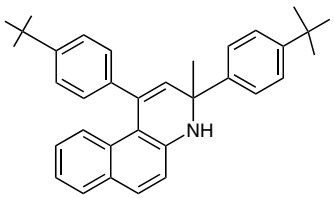
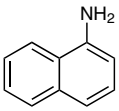
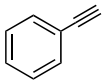
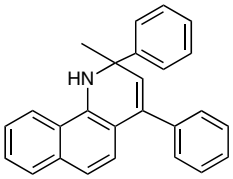
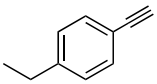
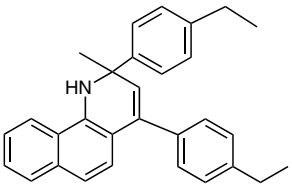
Entry	Amine **1**	Alkyne **2**	Quinoline **3**	Time (h)	Yield (%)
1	 **1a**		 **3a**	10	84
2	**1a**		 **3b**	6	82
3	**1a**		 **3c**	6	80
4	**1a**		 **3d**	7	70
5	**1a**		 **3e**	7	65
6	**1a**		 **3f**	7	50
7	**1a**		 **3g**	7	82

Table 2 Substrate Scope[a] (continued)

Entry	Amine **1**	Alkyne **2**	Quinoline **3**	Time (h)	Yield (%)
8	**1a**		 **3h**	9	62
9	 **1b**		 **3i**	10	84
10	**1b**		 **3j**	10	80

[a] Reaction conditions: amine (1 mmol), alkyne (4 mmol), $In(OTf)_3$ (10 mol%), toluene (5 mL), reflux.
[b] Isolated yield.

In summary, we have developed an efficient one-pot, three-component, tandem reaction strategy for the construction of fused quinoline derivatives in good to excellent yield. Indium(III) triflate has been shown to mediate two fundamentally different reaction steps under one-pot conditions in the absence of any other co-catalyst or additive. This methodology offers an alternate approach for the synthesis of benzo[*f*]quinolines from simple starting materials with excellent atom-economy.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(16) **Synthesis of 3a–i; General Procedure:** 2-Naphthylamine (1 mmol), alkyne (4 mmol), and $In(OTf)_3$ (0.1 mmol) were heated at reflux in toluene (10 mL) for 10 h under air. Upon completion of the reaction (as indicated by TLC), the solvent was evaporated and the crude product mixture was dissolved in chloroform and purified by column chromatography (EtOAc–hexane, 15:85) to give pure **3**.
2-Methyl-2,3-diphenyl-1,2-dihydrobenzo[*f*]quinoline (3a): Light-yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.46 Hz, 3 H), 7.61 (m, 6 H), 7.28 (m, 5 H), 7.04 (m, 2 H), 5.82 (s, 1 H), 4.72 (s, 1 H), 2.59 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.1, 142.9, 142.7, 137.1, 137.0, 133.1, 130.6, 130.1, 128.8, 128.6, 128.3, 128.2, 127.0, 126.7, 126.0, 125.3, 124.9, 121.5, 117.2, 113.1, 55.8, 26.6. IR ($CHCl_3$): 3415, 1381, 1239, 755 cm^{-1}. GC-MS: *m*/*z* = 347 $[M]^+$. Anal. Calcd for $C_{26}H_{21}N$: C, 89.88; H, 6.09; N, 4.03. Found: C, 89.98; H, 6.15; N, 4.01.

