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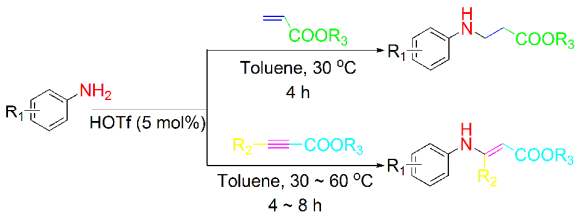

Intermolecular hydroamination of alkenes and alkynes with anilines catalyzed by HOTf under mild conditions has been developed

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ARTICLE TYPE

HOTf-Catalyzed Intermolecular Hydroamination Reactions of Alkenes and Alkynes with Anilines

Xuefeng Xu, Xu Zhang,* Zhiqiang Wang,* and Manman Kong

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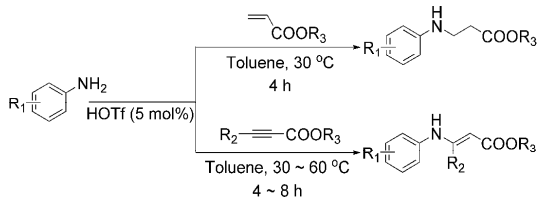
Herein, the intermolecular hydroamination of alkenes and alkynes with anilines catalyzed by HOTf under mild conditions has been developed. This reaction provides one of the simplest alkenes and alkynes addition methods and is an alternative to metal-catalyzed reactions. At the same time, the intramolecular hydroamination of alkynes with anilines proceed smothly to obtain quinolines. We found that this strategy is efficient in building complex structures from simple starting materials in an environmentally benign fashion.

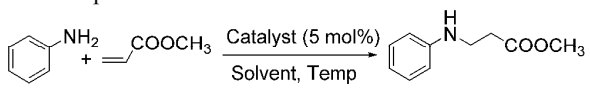
Transition metal-catalyzed carbon-heteroatom bond forming reactions are widely used in industry and academia in pharmaceutical research, materials synthesis, and process development.[1] The commonly applied methods to achieve these additions are those using either transition-metal catalysts (such as Pd, Rh, Ru, Pt, Au complexes lanthanides, actinides) or main-group metal catalysts.[2] In order to overcome the expensiveness and toxicity of transition-metal and main-group metal catalysts, the Bronsted acids have been exploited to catalyze C-O, C-C and C-N bond-formation reactions.[3] However, acid-catalyzed additions of amines to alkenes are generally unsuccessful due to the buffering effect of the amine substrate.[2, 4] Friedel-Crafts alkylations of arylamines are hindered by coordination of the amine to the Lewis acid catalyst.[5] Recentiy, Hartwig group have reports that several common Bronsted acids catalyze the intramolecular hydroamination of tosyl-protected amino olefins.[6] Beller and co-workers have reported that alkylations of electron-rich anilines with styrene are promoted with HBF_4.[7] Bergman *et al*. also described proton-catalyzed hydroamination and hydroarylation reactions of anilines and alkenes.[8] He and coworkers demonstrated that trifluoromethanesulfonic acid can catalyze the intermolecular addition of phenols, carboxylic acids, and tosylamides to unactivated alkenes under relatively mild conditions.[9] However, problems still exhibited in the present known catalytic systems. First, to the best of our knowledge, no general hydroamination procedure for a wide scope of substrates is known.[10] Terminal alkynes are usually utilized and the products are thus limited to the Markovnikov pattern while unsymmetrical (internal) alkynes are rarely reported.[11] Second, all of the aforementioned group III and lanthanide catalysts display limited functional group tolerance and high moisture sensitivity, making their routine preparation and application in synthesis problematic. Therefore, effective catalysts for the hydroamination reaction are demanded.



Scheme 1. Intermolecular hydroamination of alkenes and alkynes with anilines.

Herein we wish to report on a bronsted acid catalyzed intermolecular hydroamination of alkenes and alkynes with anilines under mild conditions. (Scheme 1). This reaction provides one of the simplest alkenes and alkynes addition methods and is an alternative to metal-catalyzed reactions and the starting materials are readily available from commercial vendors, and synthetically useful quinoline derivatives were prepared in excellent yields. This strategy is efficient in building complex structures from simple starting materials in an environmentally benign fashion.

Table 1. Optimization of reaction conditions.[a]



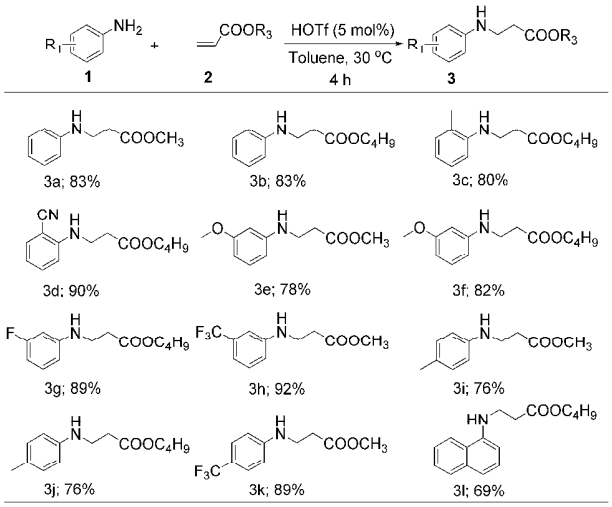
Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1	HOTf	Toluene	30	83
2	HOTf	Toluene	80	40
3		Toluene	30	NR[c]
4	HOTf	THF	30	56
5	HOTf	MeOH	30	NR
6	HOTf	CCl_4	30	NR
7	HOTf	H_2O	30	NR
8	CF_3COOH	Toluene	30	29
9	HCl	Toluene	30	NR
10	H_2SO_4	Toluene	30	NR

[a] All reactions were carried out by employing amine (1.0 mmol), alkene (1.5 mmol), and HOTf (5.0 mol%). [b]Yields after column

chromatographic purification with silica gel. [c]NR represents "the reaction does not occur."

We initially performed the reaction of the amine (1.0 mmol), and alkene (1.5 mmol) in the presence of HOTf (5 mol%) in toluene under atmospheric conditions. We were pleased to find that the reaction in toluene at 30 °C for 4 h afforded the desired product with a yield of 83% (Table 1, Entry 1). Importantly, when the temperature was raised to 100 °C, the yield was decreased to 40% for 4 h (Table 1, Entry 2). When the reaction carried out in the absence of HOTf (Table 1, Entry 3), we could not get the quinoline product. This clearly shows that the HOTf is necessary for the catalytic cycle. Solvent optimization revealed that other solvents (MeOH, CCl_4, and H_2O) are non-operative and no products could be isolated (Table 1, Entry 4, 5, 6). When the catalyst was replaced by CF_3COOH, the yield of product was dropped to 29% for 4 h, suggesting that CF_3COOH also has catalytic activity, which may be related to its acidity. No reactions occurred (Table1, Entries 8, 9) when the catalyst was changed to other acids such as HCl and H_2SO_4, emphasizing the important role played by the counterion. Following these general conditions, we then examined the scope of this reaction, and the results are summarized in Scheme 2.

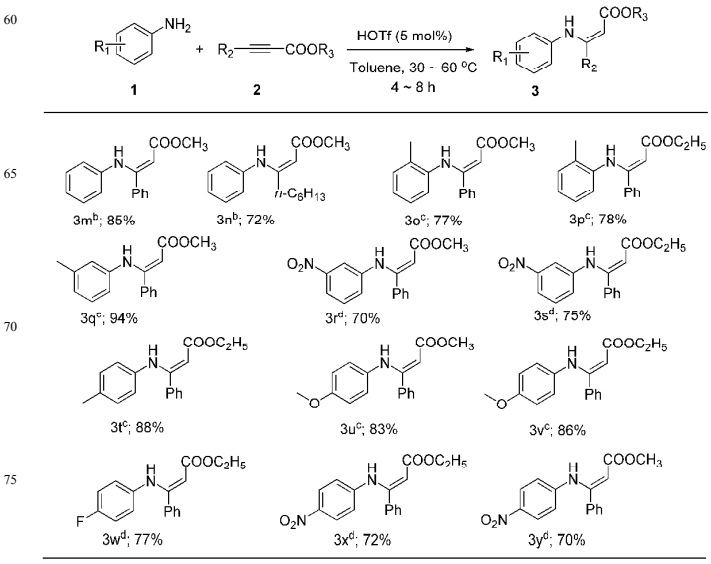
Scheme 2. Examples of secondary amine derivatives synthesis.[a]



[a]All reactions were carried out by employing amine (1.0 mmol), alkene (1.5 mmol), and HOTf (5.0 mol%). [b]Yields after column chromatographic purification with silica gel.

Under the optimized conditions, the aniline was initially used as a moderator for exploring the alkene substrate scope (Scheme 2, **3a** and **3b**). It could be seen that the alkenes with an electron-withdrawing group could give the corresponding products in good yields. The scope of aniline was also demonstrated. A variety of substituted anilines such as *ortho*-substituent (-Me and -CN), *meta*-substituents (-Me, $-OCH_3$, -F, and $-CF_3$) and *para*-substituents (-Me, and $-CF_3$) could afford good yields, as shown in Scheme 2. The electronic properties of the substituents on the aniline had some impact on the yield, which aniline with electron-donating substituents gave lower yield than that with electron-withdrawing substituents.

Scheme 3. Examples of (*Z*)-enamines derivatives synthesis.[a]



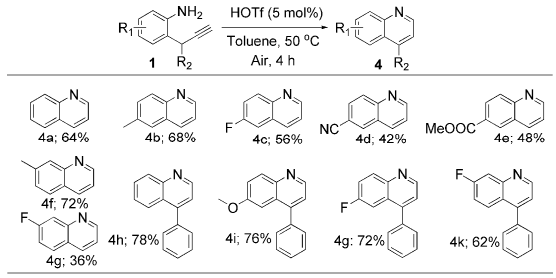
[a] All reactions were carried out by employing amine (1.0 mmol), alkyne (1.5 mmol), and HOTf (5.0 mol%); Yields after column chromatographic purification with silica gel. [b]Reaction temperature: 45 °C. [c]Reaction temperature: 60 °C. [d]Reaction temperature: 30 °C.

Next, when the alkene was replaced by alkynes, the desired products were also obtained in satisfactory yields. To show the synthetic utility of this method, a variety of amines, and alkynes were subjected to the optimized conditions. The aniline was initially used as a moderator for exploring the alkyne substrate scope (Scheme 3, **3a** and **3b**). It could be seen that the alkynes with an electron-withdrawing group could give the corresponding products in good yields. Only the (*Z*)-enamines were observed as products.[11] Alkynes with an electron-donating group also gave the products. However, the product was a mixture of regioisomers and the yield was low under the optimized conditions. The scope of aniline was also demonstrated. A variety of substituted anilines such as *ortho*-substituent (-Me), *meta*-substituents ($-NO_2$ and -Me) and *para*-substituents (-Me, -OMe, -F, and $-NO_2$) could afford good yields, as shown in Scheme 3. The electronic properties of electron-donating and electron-withdrawing substituents were perfectly suitable substrates for this transformation, and the expected products were obtained in moderate to excellent yields.

To extend the applicability of our reaction, we next turned our attention to the bronsted acid catalyzed intramolecular cyclization of an amine containing a substituted alkyne in the presence of 5 mol % of HOTf for 4 h in toluene, the results shown in Scheme 4. Under the standard reaction conditions, the substrates with electron-donating or -withdrawing groups or electron-neutral substituents were successfully transformed into the corresponding quinolines (**4a-k**). The -CN, -COOMe substituents on the aryl part of the amine (**4d/e**) were tolerated in this transformation. In

the case of **4d** and **4e**, lower yield were obtained, which might be attributed to the electronic properties of the substituent on the amine. The efficiency and functional group tolerance of this procedure have been demonstrated by synthesizing a number of substituted quinolines. This method should find numerous applications, including in the industrial field. Further investigations toward the scope of the reaction, a detailed mechanism, and applications in organic synthesis are ongoing in our laboratory.

Scheme **4** Examples of quinoline derivatives synthesis.[a]



[a]All reactions were carried out by employing substrate **1** (1.0 mmol), and HOTf (5.0 mol%) in toluene (2 ml) at 50 °C in air for 4 h. [b]Yields after column chromatographic purification with silica gel.

Conclusions

In conclusion, we have developed a bronsted acid catalyzed intermolecular hydroamination of alkenes and alkynes with anilines and intramolecular cyclization of an amine containing a substituted alkyne transformed into the corresponding quinolines under mild conditions. Some functional groups, such as the NO_2, CN substitution on arenes can be tolerated. The use of HOTf for these reactions provides a simple alternative to toxic and precious metals. The raw materials are readily available from commercial vendors, to give synthetically useful structures efficiently. The use of a single catalytic system to mediate chemical transformations in a synthetic operation is important for the development of new atom-economic strategies. We found that this strategy is efficient in building complex structures from simple starting materials in an environmentally benign fashion.

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Notes and references

[a] *School of Chemistry and Pharmacony Engineering, Nanyang Normal University, Wolong Wolong District, Nanyang City, Henan Province Road No. 1638; E-mail: zhangxuedu@126.com.*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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