

Highly Regioselective AgNTf₂-Catalyzed Intermolecular Hydroamination of Alkynes with Anilines

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Abstract: A facile and economic method for the fully regioselective and high-yielding protocol for the hydroamination of unsymmetrical internal alkynes under mild reaction conditions with AgNTf₂ was developed. The materials are easily available from commercial vendors, to give synthetically useful enamine derivatives efficiently. This strategy is efficient to build complex structures from simple starting materials in an environmentally compatible fashion.

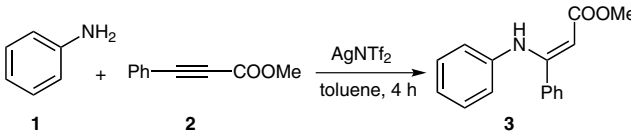
Key words: AgNTf₂ catalysis, intermolecular hydroamination, internal alkyne, enamine

Catalyzed intermolecular hydroamination of alkynes by primary amines have attracted much attention.¹ It represents one of the most atom-economic synthetic methods for substituted amines, imines, and enamines, which are important building blocks for organic compounds used as pharmaceuticals, detergents, technical additives, and dyes.² Catalysts derived from both early and late transition metals as well as lanthanides have shown significant activity for the addition of N–H bonds across a variety of alkyne moieties.^{1,2} To be of particular interest catalysts have been incorporating Pd, Ru, Au, Pt, Ir, Rh, Ni, and Ag.^{3–9} While hydroamination catalyzed by lanthanide, alkali metal, and early transition metal complexes typically take place through activation of an N–H bond, those catalyzed by late transition metal complexes, including Pd, Ru, Au, Pt, Ir, Rh, Ni, and Ag, occur through activation of C–C multiple bonds, followed by the attack of the N-

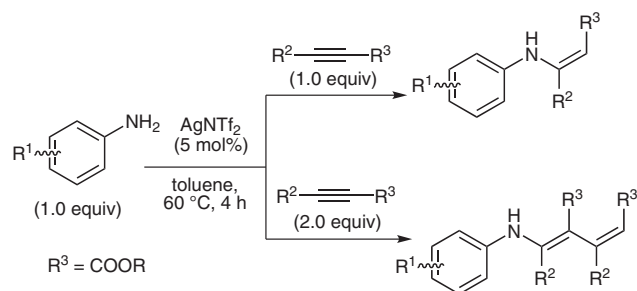
nucleophile. However, problems still exhibit in the present known catalytic systems. First, to the best of our knowledge, no general hydroamination procedure for a wide scope of substrates is known.^{1,2} Terminal alkynes are usually utilized, and the products are thus limited to the Markovnikov pattern while unsymmetrical (internal) alkynes are rarely reported.¹⁰ 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.

Herein, we report a high-yielding hydroamination protocol of internal alkynes (represented by propionate) catalyzed by AgNTf₂ under mild conditions (Scheme 1) which yields products with (Z)-enamines. The starting materials are easily available from simple commercial sources, thus affording synthetically enamine derivatives efficiently.

Table 1 Optimization of Reaction Conditions^a



Entry	Catalyst	Solvent	Temp (°C)	Yield (%) ^b
1	AgNTf ₂	toluene	25	60
2	AgNTf ₂	toluene	60	92
3	AgNTf ₂	THF	60	75
4	AgNTf ₂	MeOH	60	56
5	AgNTf ₂	CCl ₄	60	48
6		toluene	60	n.r.
7	AgOTf	toluene	60	79
8	AgCl	toluene	60	27
9	AgNO ₃	toluene	60	47



Scheme 1 AgNTf₂-catalyzed intermolecular hydroamination of alkynes with substituted anilines

^a All reactions were carried out by employing aniline (1.0 mmol), alkyne (1.0 mmol), and AgNTf₂ (5.0 mmol%).

^b Yields after column chromatographic purification with silica gel, n.r. denotes that no reaction has occurred.

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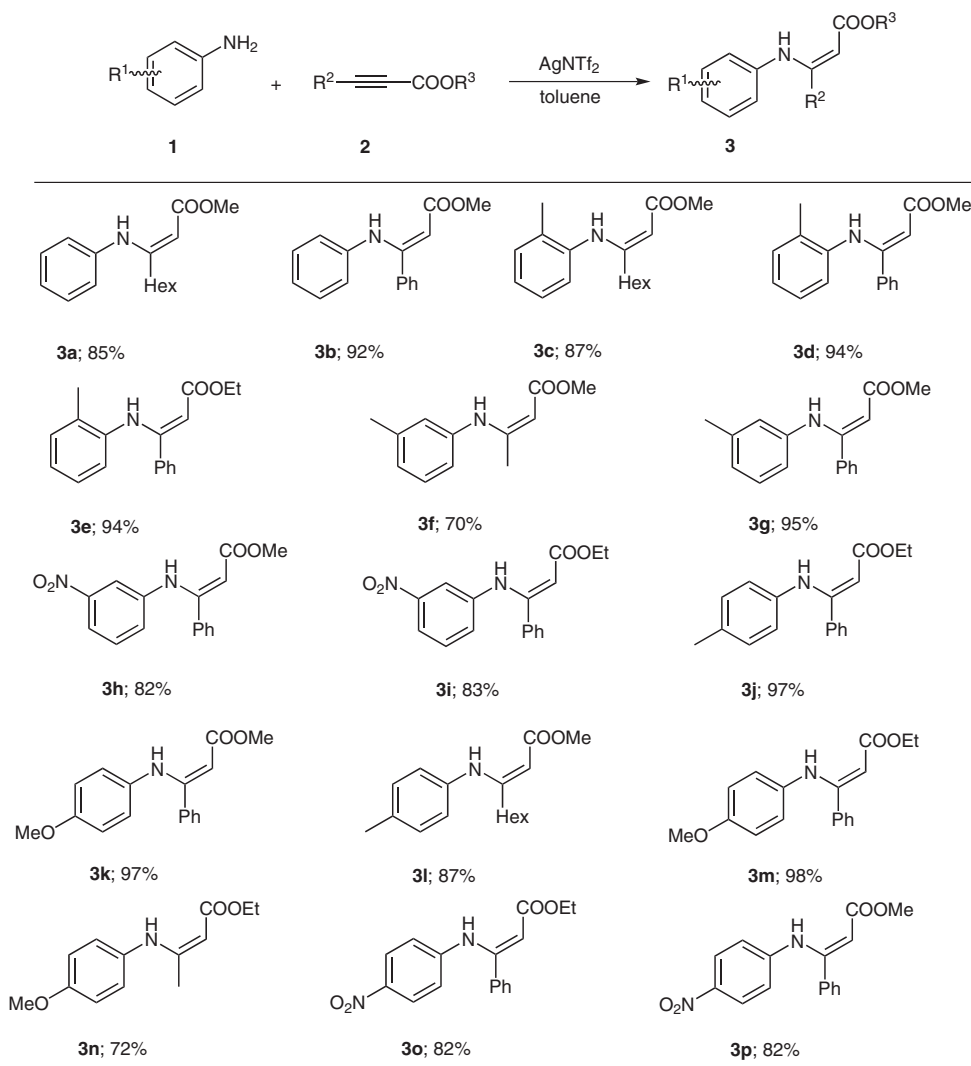
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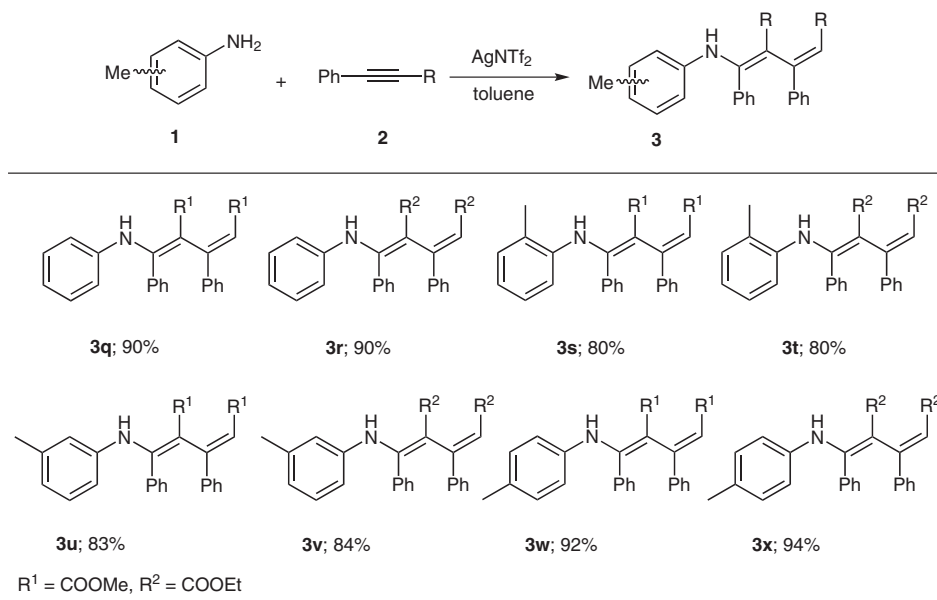
This strategy is efficient to build complex structures from simple starting materials in an environmentally compatible fashion.

To begin our study, we performed the reaction of aniline (1.0 mmol) and alkyne (1.0 mmol) in the presence of AgNTf₂ (5 mmol%) in toluene. We were pleased to find that the reaction in toluene at 25 °C for four hours afforded the desired product in 60% yield (Table 1, entry 1). Surprisingly, when the temperature was raised to 60 °C, the yield increased to 92% (Table 1, entry 2). Continued optimization revealed that other solvents (THF, CCl₄, and MeOH) all afforded the desired product, but the yields were comparatively low (Table 1, entries 3, 4, 5). When the catalyst was changed to AgOTf, the yield of the product decreased to 79% (Table 1, entry 7). Other silver catalysts (AgCl and AgNO₃), both afforded the product (Table 1, entries 8, 9). To ascertain the influence of AgNTf₂, the reaction was performed without catalyst (Table 1, entry 6), and no product was detected. Following these general conditions, we examined the scope of this reaction, and the results are summarized in Scheme 2.

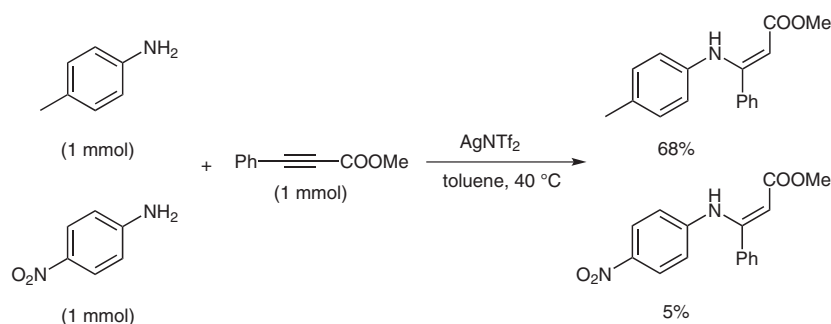
Under the optimized conditions, the aniline was initially used as a moderator for exploring the alkyne substrate scope (Scheme 2, **3a** and **3b**). It could be seen that the alkynes with an electron-withdrawing group could give the corresponding products in good yields. Only the (*Z*)-enamines were observed as products.¹⁰ The stereochemistry of the structure was also determined by NOESY spectra, which showed the cross peaks of the alkene proton with the adjacent aromatic ring. Alkynes with an electron-donating group also gave the products. However, the product was a mixture of regioisomers, and the yield was low. The regioselectivity of electron-poor alkynes was a result of the electronic effect and steric repulsion of alkynes and might primarily depend on the electronic effect.¹⁰ The scope of aniline was also demonstrated. A variety of substituted anilines – substituted with Me (*ortho*), NO₂ and Me (*meta*), and Me, OMe, and NO₂ (*para*) – could afford the corresponding products in good yields, as shown in Scheme 2. The electronic properties of the substituents on the aniline slightly affect the yield; aniline



Scheme 2 Examples of hydroamination reactions. All reactions were carried out by employing aniline (1.0 mmol), alkyne (1.0 mmol), and AgNTf₂ (5.0 mmol%) at 60 °C for 4 h. Yields after column chromatographic purification with silica gel.



Scheme 3 Examples of hydroamination reactions. All reactions were carried out by employing aniline (1.0 mmol), alkyne (2.0 mmol), and AgNTf_2 (5.0 % mmol) at 60 °C for 4 h. Yields after column chromatographic purification with silica gel.

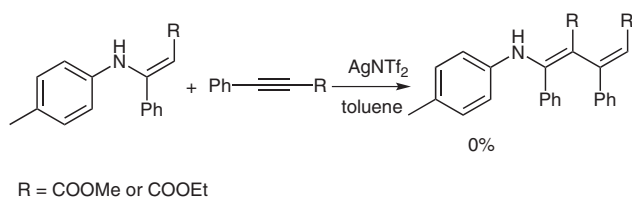


Scheme 4

with electron-withdrawing groups gave lower yield than that with electron-donating groups.

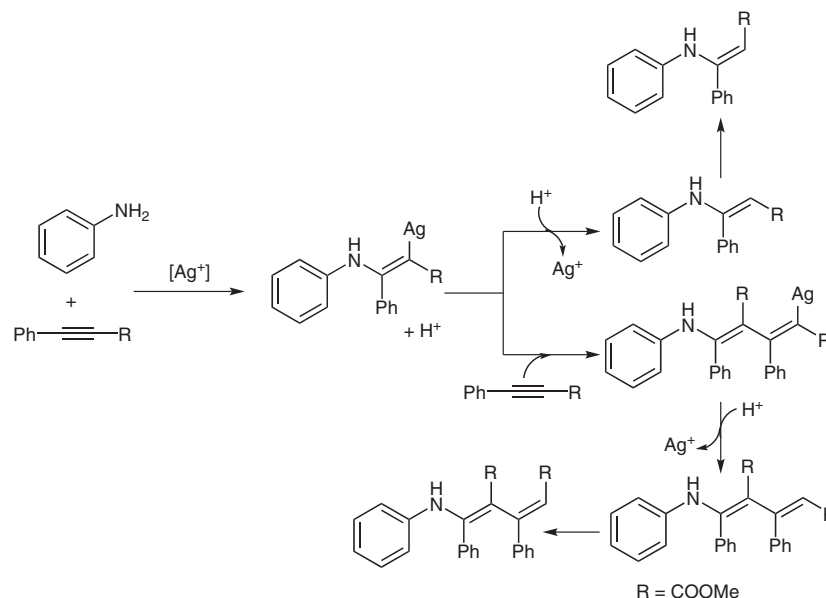
Interestingly, when two equivalents of alkynes were added, we got products as shown in Scheme 3. The electronic properties of the substituents on the anilines also affected the yields. Anilines with electron-donating substituents could afford the corresponding products in better yields, and only the (*Z*)-isomers were observed. Evidence for stereochemistry of the structure was mainly determined by the NOESY spectra, which showed the cross peaks of the alkene proton with the adjacent aromatic ring.

To gain an insight into the reaction of AgNTf_2 -catalyzed intermolecular hydroamination of alkynes with substitut-



Scheme 5

ed anilines, we first found that AgNTf_2 could not coordinate with the electron-poor alkynes, as can be seen from the ^1H NMR spectra.¹¹ Obvious change of the chemical shift from protons of aniline was observed after AgNTf_2 was added, which indicated that the catalyst might interact with aniline.^{11,12} At the same time, a deuterium exchange experiment was performed. As noted from the ^1H NMR, the integration from the NH_2 group of aniline changed from 2.01 ppm to 0.27 ppm. About 86% of the hydrogen atoms from the amine group were substituted by deuterium. This indicated that the reaction might occur through the activation of the N–H bond by AgNTf_2 , which could also be seen from the ^1H NMR spectra.¹¹ Next, under the standard conditions except that the temperature was 40 °C, both products of electron-poor *p*-nitroaniline and electron-rich *p*-methylaniline could be observed in the same reaction (Scheme 4). It could be seen that electron-richer aniline dominated the product formation, since the N–H bond on the electron-rich aniline might be activated more easily. Simultaneously, if AgNTf_2 had the similar nature with other late transition metal complexes, the activation of C–C multiple bonds might occur, followed by the attack of the N-nucleophile. The enamine might also



Scheme 6 Postulated mechanism

react with alkynes under the standard conditions to provide diene-substituted anilines (Scheme 5). Unfortunately, no conversion to the desired product was observed although the reaction proceeded for a longer time.

In light of these experiments we proposed a tentative mechanism (Scheme 6). First, the coordination of aniline with AgNTf₂ occurred, and the N–H bond was activated. The insertion of alkynes led to the generation of intermediate species, and the second alkyne could further participate in the reaction for the formation of the next intermediate. Then, the catalyst was regenerated, and the product was obtained.

In conclusion, we have developed a fully regioselective and high-yielding protocol for the hydroamination of unsymmetrical internal alkynes under mild reaction conditions catalyzed by AgNTf₂. The materials are easily available from commercial sources, to give synthetically useful enamine derivatives efficiently. This strategy is an effective method to build complex structures from simple starting materials in an environmentally compatible fashion.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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