ORGANIC LETTERS

2013
Vol. 15, No. 10
2510–2513

# Synthesis of Benzoxazoles via an Amine-Catalyzed [4 + 1] Annulation

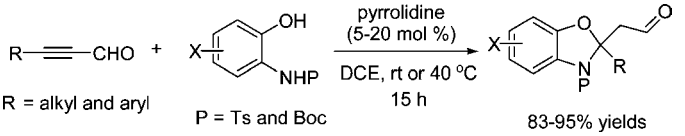
**Aiguo Song,[†] Xiaobei Chen,[†] Xixi Song,[†] Xinshuai Zhang,[†] Shilei Zhang,[†] and Wei Wang*[,†,‡]**

*Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001, United States, and School of Pharmacy, East China University of Science & Technology, Shanghai 200237, China*

*wwang@unm.edu*

**Received April 9, 2013**

## ABSTRACT




**An unprecedented simple pyrrolidine catalyzed [4 + 1] annulation reaction of ynals with *N*-protected-2-aminophenols is reported. The utilization of the unique property and reactivity of the C≡C triple bond in ynals leads to two consecutive conjugate addition reactions at the same $\beta$-position with pyrrolidine via iminium activation. The powerful cascade process affords a new alternative approach to biologically and synthetically important benzoxazoles in high yields (83−95%).**

Organocatalysis has emerged as a powerful approach to the construction of structurally diverse molecular architectures in the past decade.[1] Aminocatalysis pioneered by Barbas, List, and MacMillan has become the landmark of the field.[2,3] A number of unprecedented organic transformations have been realized with the strategy. Furthermore, capitalizing on reversible iminium-enamine catalysis, many synthetically efficient catalytic cascade processes have been developed for the facile construction of complex molecular architectures.[4] Notably, various cyclic ring structures ranging from 3 to 7 membered sizes have been constructed.[5] Despite these impressive achievements, to the best of our knowledge, there currently exists no amine catalyzed [4 + 1] annulation reaction to produce five-membered rings.[6−8] Thus, the identification of an amine catalyzed [4 + 1] annulation that is general and operationally simple remains a prominent and challenging goal. Toward this end, herein we wish to report a catalytic platform for [4 + 1] annulation. Notably, the process involving an unprecedented conjugate addition−protonation−conjugate addition cascade sequence is catalyzed by simple pyrrolidine using readily available *N*-tosyl-2-aminophenols and ynals as reactants under mild reaction conditions to

[†] University of New Mexico.
[‡] East China University of Science & Technology.

(1) (a) Berkessel, A.; Groeger, H. *Asymmetric Organocatalysis: from Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: 2005. (b) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

(2) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(3) For recent reviews of aminocatalysis, see: (a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (d) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.

(4) For selected reviews of organocatalytic cascade reactions, see: (a) Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Yu, X.-H.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2036. (c) Ayaz, M.; van Berkel, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846. (d) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237.

(5) For recent reviews on organocatalytic cyclization and cycloaddition, see: (a) Mayano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. (b) Hong, B.-C. In *Enantioselective Organocatalyzed Reactions II*; Mahrwald, R., Ed.; Springer: Dordrecht, 2011; Chapter 3, pp 187−244.

(6) Kwon et al. developed elegant phosphine-catalyzed [4 + 1] annulations with allenoate esters: (a) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928. (b) Sriramurthy, V.; Kwon, O. *Org. Lett.* **2010**, *12*, 1084. (c) Szeto, J.; Sriramurthy, V.; Kwon, O. *Org. Lett.* **2011**, *13*, 5420.

(7) Xiao et al. reported powerful sulfur ylide involved [4 + 1] annulations and cascade processes: (a) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278. (b) Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; M., Z.-H.; Xiao, W.-J. *J. Am. Chem. Soc.* **2008**, *130*, 6946. (c) Lu, L.-Q.; Li, F.; An, J.; Zhang, J.-J.; An, X.-L.; Hua, Q.-L.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9542. (d) Lu, L.-Q.; Li, F.; An, J.; Zhang, J.-J.; An, X.-L.; Hua, Q.-L.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9542. (e) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8379. (f) An, J.; Lu, L.-Q.; Yang, Q.-Q.; Wang, T.; Xiao, W.-J. *Org. Lett.* **2013**, *15*, 542.

(8) Other examples of organocatalytic [4 + 1] annulations: (a) Shi, Z.; Tan, B.; Leong, W. W. Y.; Zeng, X.; Lu, M.; Zhong, G.-F. *Org. Lett.* **2010**, *12*, 5402. (b) Guo, Z.-W.; Xie, J.-W.; Chen, C.; Zhu, W.-D. *Org. Biomol. Chem.* **2012**, *10*, 8471.

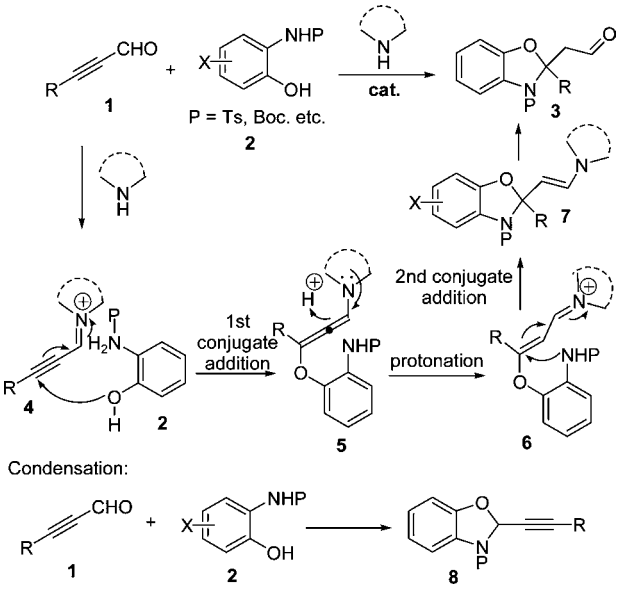
10.1021/ol400988e 
**Published on Web 05/08/2013**

give synthetically and biologically valuable benzoxazoles in high yield.[9]

Amine catalyzed 1,3-dipolar cycloaddition reactions for the formation of five-membered rings have been subjected to intensive studies.[10] In these approaches, $\alpha,\beta$-unsaturated aldehydes are genreally used as essential substrates through iminium activation with an amine promoter to react with 1,3-dipolar components such as nitrones[11] and azomethine ylides[12] in a concerted or iminium-enamine stepwise process. In contrast, the otherwise inaccessible modality, [4 + 1] annulation, offers an alternative versatile route to five-membered scaffolds because of their readily availability of starting materials. Nevertheless, a survey of literature reveals that only a handful of organocatalyzed [4 + 1] annulation reactions are reported.[6−8] Elegant examples include Kwon's phosphine promoted[6] and Xiao's sulfur ylide[7] [4 + 1] annulations.

Although iminium catalysis with enals has enjoyed great success,[3] reactions with ynals have emerged slowly. Limited examples of ynals in iminium catalysis have been reported.[13,14] This may be attributed to the similar reaction behaviors to enals, while a nonstereogenic center generated in conjugate addition adducts diminishes synthetic interest. However, recent studies reveal a number of interesting chemistries beyond the original expectation.[13,14] We have developed unprecedented chiral allenamine cascade reactions for the facile assembly of important molecular architectures, which are difficult to achieve with enal-based reactions. In our continuing effort along this avenue, we proposed a new amine catalyzed [4 + 1] cyclization reaction (Scheme 1). Given the importance of benzoxazoles in synthesis and pharmaceuticals,[9] we devised the binucleophilic *N*-tosyl-2-aminophenol substrates (**2**) for the proposed [4 + 1] annulation reaction with ynals **1**. It is hypothesized that activation of ynal **1** via iminium ion **4** renders the nucleophilic phenol −OH **2** conjugate to attack the $\beta$-position. Protonation of the resulting allenamine **5** gives a new iminium ion **6**. Then an intramolecular conjugate addition proceeds to form a benzoxazole ring **3**.

**Scheme 1.** Proposed Amine Catalyzed [4 + 1] Annulations




Although the proposed reaction appears simple, there are significant barriers to overcome. The first concern is the second conjugate reaction in the cascade. The significant steric hindrance induced by $\beta$, $\beta'$-disubstituted enals renders the conjugate addition difficult. It is even more difficult with a bulky protected "N" nucleophile. It should be noted that the examples of $\beta$, $\beta'$-disubstituted enals in aminocatalyzed conjugate additions are scarce.[15] Moreover, the "O" added adduct **5** significantly reduces the reactivity for the second conjugate addition reaction due to the formation of a deactivated electron-rich enol ether. Third, a condensation reaction between the highly active aldehyde **1** and **2** could compete with the proposed [4 + 1] process.

(9) Heterocyclic benzoxazoles are featured in numerous biologically interesting molecules. A SicFinder substructure search with benzoxazole results in more than 160 000 hits. Furthermore, bioactive indicators reveal that they have broad and important biological properties targeting the nervous system, as antitumor, -inflammatory, -infective, -diabetic, and -obesity agents and cardiovascular, immune, and respiratory mediators.

(10) Recent reviews of [3 + 2] cycloadditions: (a) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (b) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207. (c) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784.

(11) Nitrones: (a) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (b) Karlsson, S.; Hoegberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782. (c) Gonzalez-Cruz, D.; Tejedor, D.; de Armas, P.; Morales, E. Q.; Garcia-Tellado, F. *Chem. Commun.* **2006**, 2798. (d) Du, W.; Liu, Y.-K.; Yue, L.; Chen, Y.-C. *Synlett* **2008**, 2997. (e) Weselinski, L.; Stepniak, P.; Jurczak, J. *Synlett* **2009**, 2261. (f) Shen, Z.-L.; Goh, K. K. K.; Wong, C. H. A.; Loo, W.-Y.; Yang, Y.-S.; Lu, J.; Loh, T.-P. *Chem. Commun.* **2012**, *48*, 5856.

(12) Azomethine ylides: (a) Dambruoso, P.; Massi, A.; Dondoni, A. *Org. Lett.* **2005**, *7*, 4657. (b) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (c) Vicario, J. L.; Reboredo, S.; Bada, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168. (d) Ibrahem, I.; Rios, R.; Vesely, J.; Cordova, A. *Tetrahedron Lett.* **2007**, *48*, 6252. (e) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (f) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 9873. (g) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (h) Suga, H.; Arikawa, T.; Itoh, K.; Okumura, Y.; Kakehi, A.; Shiro, M. *Heterocycles* **2010**, *81*, 1669. (i) Shi, F.; Luo, S.-W.; Tao, Z.-L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 4680. (j) Sarotti, A. M.; Spanevello, R. A.; Suarez, A. G.; Echeverria, G. A.; Piro, O. E. *Org. Lett.* **2012**, *14*, 2556. (k) Shi, F.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *Chem.—Eur. J.* **2012**, *18*, 6885.

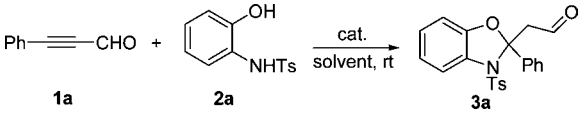
(13) We have developed organocatalytic cascade reactions with ynals: (a) Zhang, X.-S.; Zhang, S.-L.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481. (b) Liu, C.; Zhang, X.-S.; Wang, R.; Wang, W. *Org. Lett.* **2010**, *12*, 4948. (c) Zhang, X.-S.; Song, X-X.; Li, H.; Zhang, S.-L.; Chen, X.-B.; Yu, X.-H.; Wang, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 7282.

(14) Organocatalytic reactions with ynals from other research groups: (a) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (b) Alemán, J.; Núñez, A.; Marzo, L.; Marcos, V.; Alvarado, C.; Ruano, J. L. G. *Chem.—Eur. J.* **2010**, *16*, 9453. (c) Aleman, J.; Fraile, A.; Marzo, L.; Ruano, J. L. G.; Izquierdo, C.; Diaz-Tendero, S. *Adv. Synth. Catal.* **2012**, *354*, 1665. (d) Cai, X.; Wang, C.; Sun, J. *Adv. Synth. Catal.* **2012**, *354*, 359. (e) Dong, L.-J.; Fan, T.-T.; Wang, C.; Sun, J. *Org. Lett.* **2013**, *15*, 204.

(15) To the best of our knowledge, amine catalyzed conjugate additions of $\beta,\beta'$-disubstituted enals are restricted to hydrogenations: (a) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32. (b) Yang, J. W.; H. Fonseca, M. H.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108. (c) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.

To test the validity of our proposed organocatalytic [4 + 1] annulation process, we probed a model reaction of ynal **1a** with *N*-tosyl-2-aminophenol (**2a**) in the presence of simple pyrrolidine (20 mol %) as a promoter, which can readily engage in iminium formation with aldehyde functionality in ynal **1a** (Table 1). To our delight, pyrrolidine readily effects the [4 + 1] annulation reaction. The reaction proceeded smoothly to afford the desired benzoxazole **3a** in 5 min in good yield (75%, entry 1). Furthermore, under the reaction conditions, we did not observe the condensation product between aldehyde **1a** and *N*-tosyl-2-aminophenol (**2a**). It is believed that under the mild non-acidic conditions it is difficult to form the product, whose formation requires an acid promoter. In addition, it appears that the second conjugate addition reaction went smoothly. This may be due to the intramolecular process. With pyrrolidine as the catalyst, we examined the solvent effect on the process (entries 2–5). Dichloroethane (DCE) was identified as the optimal reaction medium for the reaction (entry 5). In this instance, the reaction was accomplished in 5 min to produce product **3a** in 84% yield. Furthermore, notably, lowering the catalyst loading to 5 mol % gave an even higher yield (93%) despite prolonging the reaction time (15 h) (entry 6). The increase of the yield could be explained by minimization of the undesired aldol reaction between product **3a** and reactant **1a**, which was observed with a 20 mol % catalyst loading. Importantly, no product was observed when a background reaction was carried out without any catalyst (entry 7). Besides, TEA failed to promote the reaction indicating that the [4 + 1] annulation reaction did not proceed via a base-catalyzed process (entry 8).

**Table 1.** Optimization of Reaction Conditions[a]



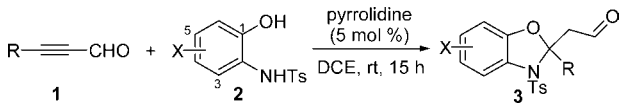

**1a** **2a** **3a**

| entry | cat. (mol %) | solvent | *t* | % yield[b] |
|---|---|---|---|---|
| 1 | pyrrolidine (20) | $CH_2Cl_2$ | 5 min | 75 |
| 2 | pyrrolidine (20) | $CHCl_3$ | 5 min | 73 |
| 3 | pyrrolidine (20) | $CH_3CN$ | 5 min | 69 |
| 4 | pyrrolidine (20) | toluene | 5 min | 61 |
| 5 | pyrrolidine (20) | $Cl(CH_2)_2Cl$ | 5 min | 84 |
| 6 | pyrrolidine (5) | $Cl(CH_2)_2Cl$ | 15 h | 93 |
| 7 | none | $CH_2Cl_2$ | 1 h | 0 |
| 8 | TEA | $CH_2Cl_2$ | 1 h | 0 |

[a] Reactions were carried out with **1a** (0.1 mmol) and **2a** (0.11 mmol) at rt in 0.2 mL of solvent. [b] Isolated yields.

The simple pyrrolidine catalyzed [4 + 1] annulation reaction serves as a general approach to structurally diverse benzoxazoles under mild reaction conditions (Table 2). The examination of the substrate scope of reactants ynals **1** has revealed a significant tolerance (entries 1–16). In addition to the unsubstituted ynal (entry 1), the aromatic ring bearing electron-withdrawing (entries 2–6) and -donating (entries 7–9) groups can be applied for the protocol. In all cases, uniformly high yields (85–93%) are achieved. Furthermore, the pyrrolidine promoted process can be extended to aliphatic (entry 10) and heterocyclic (entry 11) ynals with high efficiency. Structural variation of *N*-tosyl-2-aminophenols is then probed (entries 12–18). The catalytic system is generally applicable to a variety of *N*-tosyl-2-aminophenols under the optimized conditions. Again, high yields (83–92%) are achieved in these examples. However, interestingly it appears that the substituents on the aromatic system have an impact on the reaction. The rate of conversion with these substrates is noticeably slower than without substituents regardless of the electron-donating (entries 12–14 and 17) and -withdrawing groups that are attached (entries 15–17 and 18). Therefore, the corresponding reactions are carried out with 20 mol % catalyst and at 40 °C for 24 h to facilitate these transformations.

**Table 2.** Scope of Pyrrolidine Catalyzed [4 + 1] Annulation Reactions[a]




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

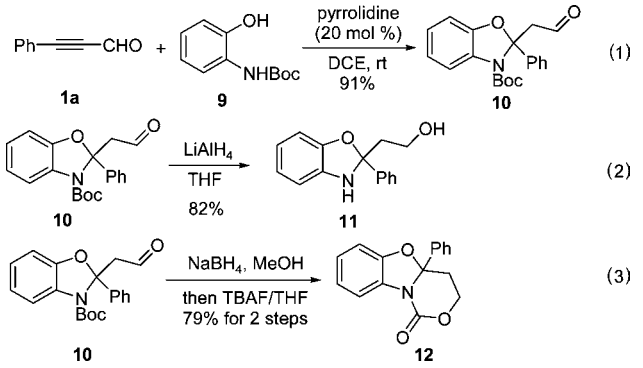
| entry | R, X | **3** | % yield[b] |
|---|---|---|---|
| 1 | Ph, H | **3a** | 93 |
| 2 | 4-$FC_6H_4$, H | **3b** | 88 |
| 3 | 4-$ClC_6H_4$, H | **3c** | 95 |
| 4 | 4-$BrC_6H_4$, H | **3d** | 92 |
| 5 | 4-$NO_2C_6H_4$, H | **3e** | 89 |
| 6 | 4-$CNC_6H_4$, H | **3f** | 85 |
| 7 | 4-$MeC_6H_4$, H | **3g** | 93 |
| 8 | 4-$MeOC_6H_4$, H | **3h** | 86 |
| 9 | 3-$MeC_6H_4$, H | **3i** | 91 |
| 10 | $BnOCH_2$, H | **3j** | 88 |
| 11 | 2-thienyl, H | **3k** | 91 |
| 12[c] | Ph, 4-Me | **3l** | 91 |
| 13[c] | Ph, 5-Me | **3m** | 89 |
| 14[c] | Ph, 4-*t*-Bu | **3n** | 83 |
| 15[c] | Ph, 4-Cl | **3o** | 87 |
| 16[c] | Ph, 4-$NO_2$ | **3p** | 84 |
| 17[c] | 4-$ClC_6H_4$, 4-Me | **3q** | 92 |
| 18[c] | 4-$NO_2C_6H_4$, 4-Cl | **3r** | 90 |

[a] Reaction conditions: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] With pyrrolidine (0.020 mmol) at 40 °C for 24 h.

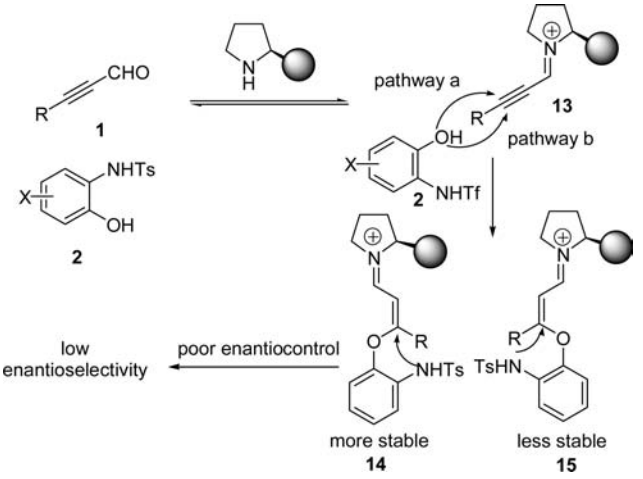
In addition, the pyrrolidine catalyzed [4 + 1] annulation reaction can be applied with Boc-protected 2-aminophenol **9** (Scheme 2, eq 1). Under similar reaction conditions with 20 mol % catalyst, the process proceeded smoothly to afford the desired product **10** in 91% yield. The [4 + 1] annulation product **10** can be deprotected to give **11** by reduction with $LiAlH_4$ in 82% yield (eq 2). Furthermore, reduction of **10** to alcohol by $NaBH_4$ followed by treatment with TBAF afforded the cyclization product **12** in 79% yield in a two-step transformation (eq 3).

Having demonstrated a simple pyrrolidine catalyzed [4 + 1] annulation reaction of ynals with *N*-tosyl/Boc-2-aminophenols, we attempted to probe a catalytic enantioselective version with a chiral organocatalyst (Table S1 in SI).

**Scheme 2.** Synthetic Elaboration of [4 + 1] Annulation Products

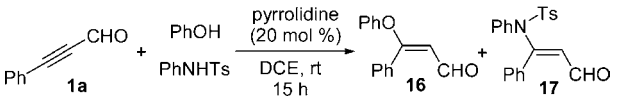



**Scheme 3.** Rationalization of Low Enantioselectivity of Chiral Amine Catalyzed [4 + 1] Annulation




Disappointingly, very poor ee's were observed in these cases. The observed results could be rationalized in the proposed model (Scheme 3). The "O"-centered nucleophilic species in **2** is involved in the first conjugate addition (see below preliminary mechanistic study). The nucleophilic addition could proceed in two possible ways, pathways a and b, due to the linear geometry of the C≡C triple bond and lead to respective adducts **14** and **15**. Compound **14** is believed to be formed more favorably since the "O" attacks the less steric side of a chiral amine derived iminium ion **13**. Furthermore, the bulky NHTs moiety in **14** and **15** is oriented in position to minimize the interaction with the big side chain of the catalyst. The new stereogenic center is created in the second conjugate addition. However, the chiral center of the catalyst (e.g., **14** and **15**) is far away from the conjugate addition reaction center in both cases. Accordingly, it is expected that poor enantiocontrol is observed in both chiral iminiums **14** and **15**. This is also evidenced in the chiral amine catalyzed nuelcophilic conjugate addition of $\beta,\beta'$-disubstituted $\alpha,\beta$-unsaturated aldehydes. A very limited number of examples exhibiting good enantioselectivity have been reported.[15]

**Table 3.** Addition Sequence Tests of [4 + 1] Annulation Reactions[a]




| entry | PhOH | PhNHTs | % yield[b] | % yield[b] |
|---|---|---|---|---|
| 1 | 1.1 equiv | 0.0 equiv | 92 | 0 |
| 2 | 0.0 equiv | 1.1 equiv | 0 | 0 |
| 3 | 1.1 equiv | 1.1 equiv | 90 | 0 |

[a] Reaction condition: a mixture of PhOH (0.11 mmol) and/or PhNHTs (0.11 mmol), **1a** (0.1 mmol), and pyrrolidine (0.005 mmol) in 0.5 mL of DCE was stirred at rt for 15 h. [b] Isolated yields.

Although the addition sequence of "O" and "N" nucleophiles does not affect the structures of the reaction products, the studies may help to understand their nucleophilic nature. Furthermore, such insight may also assist in developing an asymmetric version of the process. Under the same reaction conditions we employed above (Table 3), we performed the conjugate addition reactions of alkynal **1a** with PhOH or PhNHTs, respectively. Oxo-conjugate addition adduct **16** was formed in 92% yield (entry 1), while no detectable aza-conjugate addition product **17** was observed (entry 2). The competition reaction between PhOH and PhNHTs furthermore confirmed that the O nucleophile in **1** should be added to alkynals first (entry 3). The "O" addition occurred first which may be due to less hindrance. The results could help us to develop an asymmetric synthesis of enantioenriched benzoxazoles where the second conjugate addition is responsible for the formation of a stereogenic center.

In conclusion, we have designed and implemented an unprecedented amine-catalyzed [4 + 1] annulation reaction. The notable features of the process include a new conjugate addition−protonation−conjugate addition cascade sequence by employing readily available ynals and *N*-protected-2-aminophenols as reactants. Moreover, an iminium-allenamine-iminium activation mode promoted by simple pyrrolidine is reported for the first time. The mild reaction protocol allows for a broad spectrum of ynals and 2-aminophenols to engage in the cascade sequence with high efficiency. Furthermore, synthetically and biologically important benzoxazoles are created in a one-pot operation. The development of enantioselective [4 + 1] annulation reactions for the formation of enantioenriched benzoxazoles and expansion of the activation mode using underexplored ynals in aminocatalysis are being pursued in our laboratory.

**Acknowledgment.** Financial support from the NSF (CHE-1057569) and East China University of Science and Technology is gratefully acknowledged.

**Supporting Information Available.** Experimental procedures; $^{1}H$, $^{13}C$ NMR and HRMS data for **2**, **3**, **10**−**12**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.