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$Zn(OTf)_2$-Catalyzed Cyclization of Proparyl Alcohols with Anilines, Phenols, and Amides for Synthesis of Indoles, Benzofurans, and Oxazoles through Different Annulation Mechanisms

Manyam Praveen Kumar and Rai-Shung Liu*

Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan 30043

rsliu@mx.nthu.edu.tw

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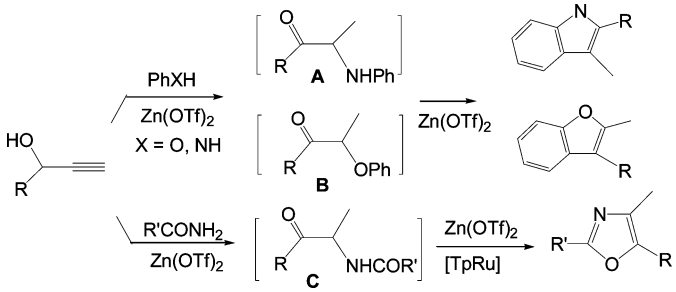

$Zn(OTf)_2$ (10 mol %) catalyzed the cyclization of propargyl alcohols with PhXH (X = O, NH) in hot toluene (100 °C) without additive and gave indole and benzofuran products with different structures. In such transformations, α-carbonyl intermediates **A** and **C** were isolated as reaction intermediates. The 1,2-nitrogen shift in the formation of indole is catalyzed by $Zn(OTf)_2$, and its mechanism has been elucidated. This catalytic cyclization is also applicable to the synthesis of oxazoles through the cyclization of propargyl alcohols and amides without a 1,2-nitrogen shift.

Introduction

Indoles and benzofurans are important functionalities in many pharmacologically active molecules. Metal-catalyzed synthesis of such heteroaromatic compounds has received considerable attention.[1−8] Most documented methods involve the use of starting α-functionalized anilines or phenols, which are expensive and not readily available.[3−8] The use of propargyl alcohol as a two-carbon building unit for synthesis of heteroaromatic compounds is practical and intriguing in mechanistic aspects. There are two distinct pathways depending on the types of catalysts: (a) an initial propargyl at the C(3)-carbon[8a,9] or (b) amination at the C(2)-carbon[10] with a subsequent annulation. These two catalytic methods have been applied to the synthesis of furans,[9] oxazoles,[8a] and indoles,[10] and their reaction protocols

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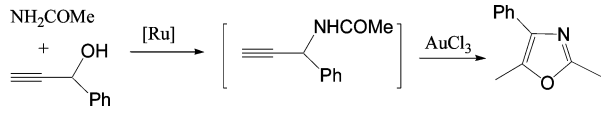
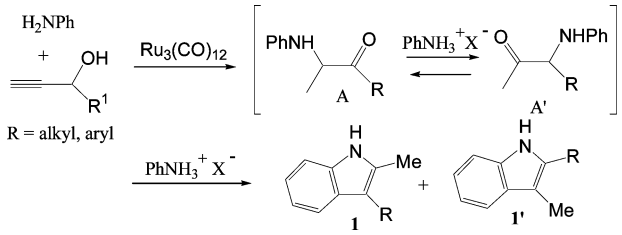
SCHEME 1



SCHEME 2



are shown in Schemes 1 and 2, respectively. One drawback for such cyclizations is the use of two catalysts, one to achieve nucleophilic addition at alkynes and another for a subsequent cyclization of the resulting intermediates.[9,10] In the second process,[10] $Ru_3(CO)_{12}$ is responsible for the initial C(2)-amination of propargyl alcohols, whereas additive $PhNH_3X$ catalyzes both the isomerization between two α-aminoketone **A** and **A′**[11] as well as the cyclization of these two intermediates. This catalytic process produces two indole regioisomers with a 1,2-nitrogen migration product **1′** being dominant (**1′**/**1** > 6.0).

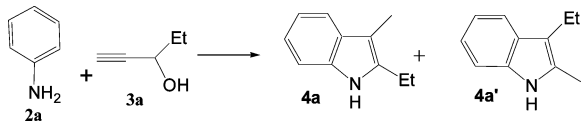
Here, we report a new $Zn(OTf)_2$-catalyzed synthesis of indoles, benzofurans, and oxazoles using propargyl alcohols as a two-carbon building unit. In contrast with preceding examples, $Zn(OTf)_2$ activates both the C(2)-addition of propargyl alcohols and their subsequent cyclizations. Only one regioisomeric product is obtained for these heteroaromatic compounds, but indole derivatives are distinct from oxazoles and benzofurans in cyclization regioselectivity.

Results and Discussions

In a typical operation, aniline **2a** was heated with neat 1-pentyn-3-ol **3a** in equal proportion (130 °C, 4 h) in the presence of $Zn(OTf)_2$ (10 mol %), giving two isomeric indoles **4a** and **4a′** (**4a**/**4a′** = 4.5) as shown in Table 1. The structure of species **4a** was indicated by ^{1}H-NOE and confirmed by comparison of its NMR data to those of authentic samples.[12] The use of benzene and toluene as reaction solvents in a sealed tube gave only indole **4a** according to NMR analysis (entries 2 and 3). This $Zn(OTf)_2$-catalyzed cyclization is highly sensitive to solvents, and starting aniline was recovered in 68% and 75% yield using dichloroethane (DCE) and dimethoxyethane (DME) as solvents (entries 4 and 5). Among other π-alkyne activators (entries 6−8), only $Cu(OTf)_2$ were found to be equally efficient for such indole synthesis (86% yield).

Table 2 shows additional examples of the $Zn(OTf)_2$-catalyzed indole synthesis using various anilines and propargyl alcohols. Entries 1−4 show the applicability of this cyclization to propargyl alcohols **3b**−**e** bearing various R substituents (R =

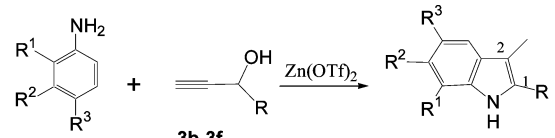
TABLE 1. $Zn(OTf)_2$-Catalyzed Synthesis of Indole Derivatives



entry	catalyst[a]	solvent	*T*, °C (time, h)	product (yield, %)[b]
1	$Zn(OTf)_2$		130 (4)	**4a**/**4a′** = 4.5 (95)
2	$Zn(OTf)_2$	benzene	100 (14)	**4a** (89)
3	$Zn(OTf)_2$	toluene	100 (8)	**4a** (97)
4	$Zn(OTf)_2$	DCE	100 (14)	N.R.
5	$Zn(OTf)_2$	DME	100 (14)	N.R.
6	$AuCl_3$	toluene	100 (14)	
7	$PtCl_2$	toluene	100 (14)	
8	$Cu(OTf)_2$	toluene	100 (14)	

[a] 10 mol % of catalyst, [substrate] = 1.3 M. [b] Products were separated from a silica column.

TABLE 2. $Zn(OTf)_2$-Catalyzed Synthesis of Indole



entries	aniline[a]	alcohol	products[b] (yields)
1	R^1 = R^2 = R^3 =H (**2a**)	R = ^{i}Pr (**3b**)	4b (71%)
2	**2a**	R = ^{i}Bu (**3c**)	**4c** (92%)
3	**2a**	R = Ph (**3d**)	**4d** (91%)
4	**2a**	R = 2-Np (**3e**)	**4e** (90%)
5	R^2 = R^3 =H, R^1 = Me (**2b**)	**3d**	**4f** (90%)
6	R^1 = R^2 =H, R^3 = Me (**2c**)	**3d**	**4g** (78%)
7	R^1 = R^3 =H, R^2 = Me (**2d**)	**3d**	**4h** (93%)
8	R^1 = R^2 =  , R^3 = H (**2e**)	**3d**	**4i** (93%)

[a] 10 mol % of catalyst, toluene, 100 °C, [substrate] = 1.1 M. [b] Products were separated from a silica column.

(6) Benzofuran synthesis using palladium catalysts: (a) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed*. **2004**, *43*, 6144. (b) Willis, M. C.; Taylor, D.; Gilmore, A. T. *Org. Lett*. **2004**, *6*, 4755. (c) Hu, Y.; Nawoschik, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235. (d) Youn, S. W.; Eom, J, I. *Org. Lett*. **2005**, *7*, 3355. (e) Xie, X.; Chen, B.; Lu, J.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett*. **2004**, *45*, 6235. (f) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.

(7) Benzofuran synthesis using other metal catalysts: (a) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc*. **2005**, *127*, 15024. (b) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett*. **2005**, *7*, 5437. (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc*. **2005**, *127*, 15022. (d) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292.

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(9) (a) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681. (b) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yohsikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. Eur. J*. **2005**, *11*, 1433.

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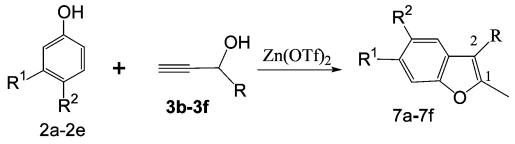
TABLE 3. Zn(OTf)$_2$-Catalyzed Synthesis of Benzofurans



entries	phenol	alkynol	products (yields)
1	$R^1 = R^2 =$ H (**6a**)	R = Ph (**3d**)	**7a** (86%)
2	R^1 =H, R^2 =OMe (**6b**)	**3d**	**7b** (91%)
3	$R^1 = R^2 =$  (**6c**)	**3d**	**7c (95%)**
4	$R^1 = R^2 =$  (**6d**)	**3d**	**7d (92%)**
5	R^1 =H, R^2 =Me (**6e**)	R = 4-FC_6H_4 (**3f**)	**7e (85%)**
6	**6c**	R =  (**3g**)	**7f (94%)**

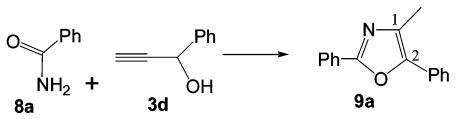
[a] 10 mol % of catalyst, toluene, 100 °C, [substrate] = 0.75 M. [b] Products were separated from a silica column.

^{i}Pr, ^{i}Bu, Ph, 2-naphthyl); the resulting indole products **4b**−**e** were obtained in 71−91% yields. Entries 5−7 show the compatibility of this method with various anilines **2b**−**d** having a methyl at the C(2), C(3), and C(4) positions; the corresponding indole products **4f**−**h** were obtained in 78−93% yields. This indole synthesis is successfully extensible to 1-aminonaphthalene, which gave indole **4i** in 93% yield (entry 8). The structure of **4b** was identified by ^{1}H-NOE spectra,[13] whereas the molecular structure of compound **4h** has been elucidated by X-ray diffraction methods.[14]

We extended this Zn(OTf)$_2$-catalyzed cyclization to catalytic synthesis of benzofurans using phenols and propargyl alcohols, and the examples are summarized in Table 3. Cyclization of phenol **6a** with 3-phenyl-1-propyn-3-ol **3d** using Zn(OTf)$_2$ (10 mol %) in hot toluene (100 °C, 16 h) afforded benzofuran **7a** in 86% yields (entry 1). This method is compatible with various phenols **6b**, **6c**, and **6d**, which gave the corresponding benzofurans **7b**, **7c**, and **7d** with yields exceeding 91% (entries 2−4). Entries 5 and 6 provide additional examples for cyclization of various 3-phenyl-1-propyn-3-ols **3f** and **3g** with suitable phenols, which gave desired products **7e** and **7f** in 85−94% yields. Among these benzofurans, the structure of species **7a** was identified by ^{1}H-NOE effects;[13] its NMR spectra are consistent with literature data.[15] These benzofurans differ notably from indole products in their structures because the former has a C(1)-methyl and the latter has a C(2)-methyl group.

The value of this Zn(OTf)$_2$-catalyzed reaction is demonstrated also by its applicability to the synthesis of oxazoles through the cyclization of propargyl alcohols with amides. As shown in Scheme 3, treatment of 3-phenyl-1-propyn-3-ol with benzamide with Zn(OTf)$_2$ (10 mol %) in hot toluene (100 °C) gave oxazole **9a** in only 28% yield, but the presence of cocatalyst TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ (10%)[16] greatly enhanced the catalytic activity, giving oxazole with 95% yield. Use of TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ alone in catalytic cyclization led only to the recovery

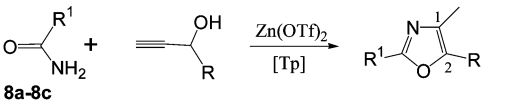
SCHEME 3



entries	catalysts[a]	conditions	yields[b]
1	Zn(OTf)$_2$	100 ^{0}C, 22 h	28%
2	Zn(OTf)$_2$/[TpRu]	100 ^{0}C, 5 h	95%
3	[TpRu]	130 ^{0}C, 20 h	N. R.

[a] [TpRu] = TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$; 10 mol % of catalyst, toluene, 100 °C, [substrate] = 0.75 M. [b]Products were separated from a silica column.

TABLE 4. Zn(OTf)$_2$-Catalyzed Synthesis of Oxazole Derivatives



entries	amide	alkynol	products (yields)
1	R^1 = Ph (**8a**)	R = 4-FC_6H_4 (**3f**)	**9b** (90%)
2	**8a**	R = 4-MeC_6H_4 (3h)	**9c** (88%)
3	**8a**	R = 4-$OMeC_6H_4$ (**3i**)	**9d** (94%)
4	**8a**	R =  (**3g**)	**9e** (95%)
5	R^1 = n-C_5H_{11} (**8b**)	**3i**	**9f** (90%)
6	R^1 =  (**8c**)	**3i**	**9g** (95%)

[a] 10 mol % of catalyst, toluene, 100 °C, [substrate] = 0.75 M. [b] Products were separated from a silica column.

of starting amide **8a** and propargyl alcohol **3d**. These results indicate that Zn(OTf)$_2$ is responsible for the C(2)-amination of propargyl alcohols and that TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ is more active for the subsequent cyclization.

Table 4 shows a generalization of the catalytic oxazole synthesis with various amides and propargyl alcohols; the reactions were performed in hot toluene (100 °C, 5 h) using Zn(OTf)$_2$ and TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ at 10 mol % loading. Entries 1−4 include additional examples for the cyclization of benzamide **8a** with various 3-phenyl-1-propyn-3-ols **3f**−**i**, which gave oxazole products **9b**−**e** with yields up to 88−95%. Entries 5 and 6 show the applicability of this catalytic reaction to *n*-caproamide **8b** and 2-methylacrylamide **8c**, and the corresponding oxazoles **9f**,**g** were obtained in 90% and 95% yields, respectively. The structure of oxazole **9c** has been characterized by X-ray diffraction study,[14] which reveals that these oxazole products closely resemble benzofurans **7a**−**f** in their skeletal structure; both compounds have a methyl group at the C(1) carbon, which is the carbon being attacked by phenol and amide nucleophiles. In contrast, indole derivatives **4a**−**h** have a methyl group located at the C(2)-carbon, rather than the C(1)-carbon.

Scheme 4 shows our efforts to elucidate the reaction mechanism of the indole synthesis via isolation of reaction intermedi-

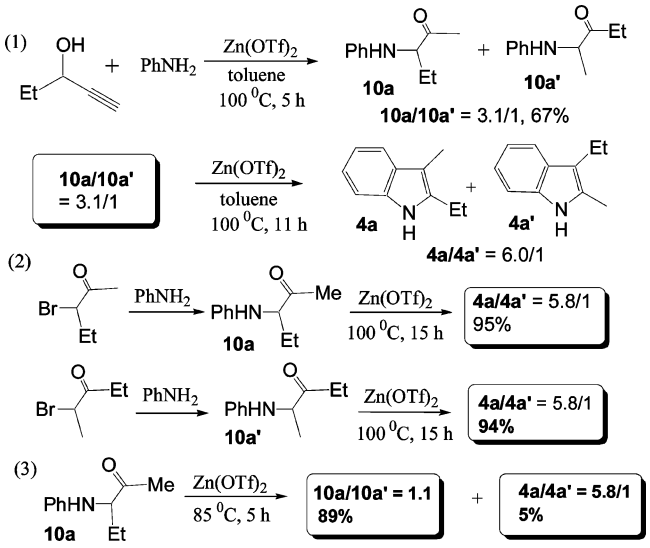
(13) The ^{1}H NOE effects of key compounds **4a**, **4b**, **7a**, and **7b** are provided in the Supporting Information.

(14) The X-ray structural data of compounds **4h** and **9c** are provided in the Supporting Information.

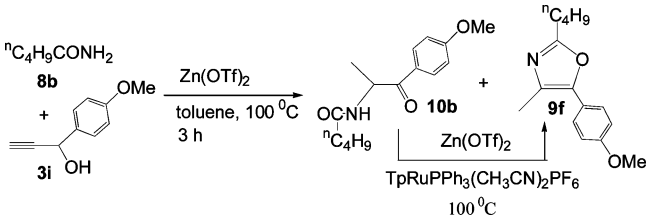
(15) Katritzky, A. R.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613.

(16) TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ is considered to be a mild Lewis acid; see the following examples of catalysis using this catalyst: (a) Chan, W.-C.; Lau, C.-P.; Chen, Y.-Z.; Fang, Y.-Q.; Ng, S.-M.; Jia, G. *Organometallics* **1997**, *16*, 34. (b) Madhushaw, R. J.; Lin, M.-Y.; Abu Sohel, S. M.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 6895. (c) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *12*, 3406. (d) Lin, M.-Y.; Maddirala, S. J.; Liu, R.-S. *Org. Lett.* **2005**, *7*, 1745.

SCHEME 4



SCHEME 5

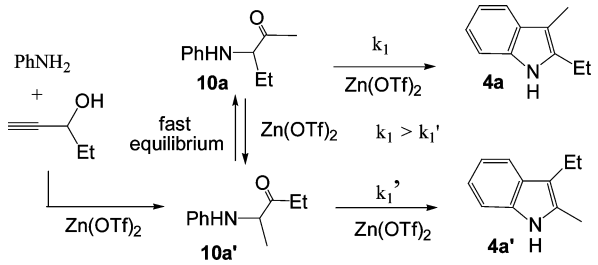


ates after brief periods of reactions. As depicted in eq 1, treatment of pen-1-tyn-3-ol **3a** with aniline **2a** and $Zn(OTf)_2$ (10 mol %) in hot toluene for a brief period (100 °C, 5 h) gave a mixture of isomeric ketones **10a** and **10a′** (**10a′**/**10a** = 3.1, 67%), indicating that the indole synthesis is initiated by a C(2)-amination of an alcohol. In this case, two isomeric α-amino ketones **10a** and **10a′** (**10a**/**10a′** = 3.1) were obtained, and this mixture was isolated, purified, and subsequently heated with $Zn(OTf)_2$ (10 mol %) in hot toluene (100 °C, 11 h), eventually yielding two isomeric indoles **4a′** and **4a** in 95% yields (**4a**/**4a′** = 6.0). In separated experiments, we succeeded in obtaining a single α-amino ketone **10a** or **10a′** according to the protocol in eq 2 (Scheme 4). Notably, these two α-amino ketones notably produced the same composition of indoles **4a′** and **4a** efficiently upon heating each species alone with$Zn(OTf)_2$. After a brief period (85 °C, 5 h), we found that species **10a** became isomerized to the other α-amino ketones **10a′** in a ratio of **10a**/**10a′** = 1.1. These observations imply that $Zn(OTf)_2$ is active not only for cyclization of α-amino ketones **10a** or **10a′** to give mainly indole **4a′** but also for rapid isomerization between α-amino ketones **10a** and **10a′**.

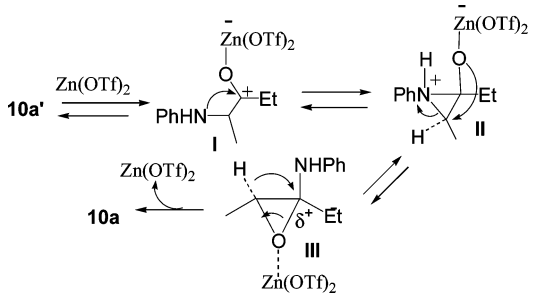
We also elucidated the mechanistic pathway for $Zn(OTf)_2$-catalyzed synthesis of benzofurans and oxazoles, which have different structures from indole synthesis. As shown in Scheme 5, heating a mixture of amide **8b** with alcohol **3i** with $Zn(OTf)_2$ in hot toluene (100 °C, 3 h) produced α-carbonyl amide **10b** (64%) and oxazole **9f** (27%). In contrast with the indole synthesis, we found no other isomeric α-carbonyl amide corresponding to a 1,2-nitrogen shift. Heating compound **10b** with $Zn(OTf)_2$ (10 mol %) and $TpRuPPh_3(CH_3CN)_2PF_6$ (10 mol %) gave only oxazole **9f** in 96% yield.

In the indole synthesis, species **4a** arises primarily from intramolecular cyclization of α-amino ketone intermediate **10a**

SCHEME 6



SCHEME 7



catalyzed by $Zn(OTf)_2$. This hypothesis is supported by Zn-$(OTf)_2$-catalyzed conversion of α-carbonyl amide **10b** to oxazole **9f** as depicted in Scheme 5. The $Zn(OTf)_2$-catalyzed isomerization between species **10a** and **10a′** is remarkable since we observed no analogous reaction in the oxazole and benzofuran synthesis. This isomerization mechanism differs from those using $PhNH_3X$ catalyst in the $Ru_3(CO)_{12}$-catalyzed indole synthesis as depicted in Scheme 2. Scheme 6 rationalizes the observed chemoselectivity in indole synthesis. The equilibrium between α-amino ketones **10a** and **10a′** is thought to be fast and reversible according to our observation in Scheme 4. The preference for formation of indole **4a** is the faster rate in cyclization of ketone **10a** relative to that of its regioisomer **10a′** ($k_1 > k_1'$). Scheme 7 also shows a plausible mechanism for mutual isomerization between ketones **10a** and **10a′**. We propose that $Zn(OTf)_2$ initially coordinates to ketone **10a′** to generate carbocation (**I**), and this species subsequently produces aziridine intermediate (**II**) via an intramolecular nitrogen attack. The R_3-NH^+ functionality of species (**II**) enhances the opening of an aziridine ring via its tethered oxygen attack, giving epoxide (**III**), which ultimately yielded the other α-haloketone **10a** following the epoxide−ketone rearrangement.[17] Relative to phenol and amide nucleophiles, the aniline nitrogen has a greater nucleophilicity to generate aziridine intermediate **I**, which might account for the observed 1,2-nitrogen shift in the indole synthesis.

Conclusion

With $Zn(OTf)_2$ as catalyst, we achieved synthesis of indole, benzofuran, and oxazole through cyclization of propargyl alcohols with anilines, phenols, and amides. The skeletal structures of indole products differ from those of benzofurans and oxazoles. We have elucidated the mechanism of formation of indole and oxazole products, in which $Zn(OTf)_2$ catalyzes the C(2)-addition of aniline and amide nucleophiles to propargyl alcohol moieties. For indole formation, $Zn(OTf)_2$ is active for

(17) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Part 3.3, p 733.

not only the intramolecular cyclization of α-amino ketone intermediates but also for the isomerization of α-amino ketone intermediates through a 1,2-nitrogen shift. Zn(OTf)$_2$ shows similar reaction pathways for benzofuran and oxazole syntheses except that the resulting α-carbonyl intermediates do not undergo isomerization in the presence of Zn(OTf)$_2$ catalyst.

Experimental Section

(1) Procedure for Catalytic Synthesis of Indole (4a). To a toluene solution (0.80 mL) of aniline (132 mg, 1.4 mmol) were added pent-1-yn-3-ol (**3a**) (100 mg, 1.1 mmol) and zinc triflate (43 mg, 0.01 mmol); the reaction mixture was heated at 100 °C for 8 h. The solution was filtered over a short silica bed, washed with diethyl ether (5 mL), and concentrated under reduced pressure to afford 3-ethyl-2-methyl-1*H* indol (**4a**) as colorless crystals (mp 38−40 °C, 184 mg, 1.15 mmol, 97%): IR (neat, cm^{-1}) 3418 (s), 3041 (w), 1569 (s), 1609 (w), 1371 (s), 1087 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (br, 1H), 7.55 (dd, J = 6.8, 2.4 Hz, 1H), 7.28 (dd, J = 6.8, 2.4 Hz, 1H), 7.12−7.20 (m, 2H), 2.76 (q, J = 8.0 Hz, 2H), 2.29 (s, 3H), 1.31 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 135.0, 129.4, 120.8, 118.9, 117.9, 110.1, 106.0, 19.3, 13.9, 8.2; HRMS calcd for $C_{11}H_{13}N$ 159.1048, found 159.1047.

(2) Procedure for Catalytic Synthesis of Benzofuran (7a). To a toluene solution (0.80 mL) of phenol (87 mg, 0.92 mmol) were added 1-phenyl-prop-2-yn-1-ol (**3d**) (100 mg, 0.75 mmol) and zinc triflate (27 mg, 0.075 mmol); the reaction mixture was heated at 100 °C. The reaction was monitored by TLC. After completion, the reaction mixture was filtered over a short silica bed and concentrated under reduced pressure to give 2-methyl-3-phenyl-benzofuran (**7a**) as colorless plates (mp 93−95 °C (lit.[8b] mp 93−95 °C), 136 mg, 0.65 mmol, 86%): IR (neat, cm^{-1}) 3417 (s), 3046 (w), 2973 (w), 1602 (s), 1379, 1261 (m), 743 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.56 (d, J = 8.4 Hz, 1H), 7.51−7.43 (m, 5H), 7.37−7.33 (m,1H), 7.27−7.19 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0, 151.2, 132.8, 128.9, 128.7, 126.5, 123.5, 122.5, 119.3, 116.8, 110.7, 12.8; HMRS calcd for $C_{15}H_{12}O$ 208.0888, found 208.0884.

(3) Procedure for Catalytic Synthesis of Oxazole (9a). To a toluene solution (0.80 mL) of benzamide (**8a**) (110 mg, 0.90 mmol) were added 1-phenylprop-2-yn-1-ol (**3d**) (100 mg, 0.75 mmol), zinc triflate (27 mg, 0.075 mmol), and $TpRuPPh_3(CH_3CN)_2PF_6$ (57 mg, 0.075 mmol), and the reaction mixture was heated at 100 °C for 5 h. The solution was filtered over a short silica bed and concentrated under reduced pressure to give 4-methyl-2,5-diphenyloxazole (**9a**) as colorless crystals (mp 77−79 °C (lit.[15] 78−80 °C), 170 mg, 0.72 mmol, 95%): IR (neat, cm^{-1}) 3349(w), 3038(m), 2936(s), 1636-(w), 1612(w), 1583(w), 1377(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 7.8, 1.2 Hz, 2H), 7.72 (dd, J = 7.8, 1.2 Hz, 2H), 7.45 ∼ 7.41 (m, 6H), 2.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 143.9, 135.9, 132.2, 129.9, 128.6, 128.5, 127.6, 127.2, 126.8, 126.1, 11.9; HMRS calcd for $C_{16}H_{13}NO$ 235.0997, found 235.0998.

(4) Procedure for Preparation of α-Amino Ketone (10a). To an aqueous ethanol (5 mL) solution of 3-bromopentan-2-one[18] (500 mg, 3.03 mmol) were added aniline (338 mg, 3.63 mmol), sodium bicarbonate (305 mg, 3.63 mmol), and water (65 mg, 3.63 mmol), and the reaction mixture was heated at 80 °C for 10 h. The solvent was evaporated, extracted with diethyl ether, dried over $MgSO_4$, concentrated, and finally chromatographed through a silica column to give 3-phenylaminopentan-2-one (**10a**) as a yellow oil (430 mg, 2.42 mmol, 80%): IR (neat, cm^{-1}) 3419 (s), 3048 (w), 1718 (s), 1617 (w), 1568 (s), 1376 (s), 1141 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, J = 7.6 Hz, 2H), 6.69 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 7.6 Hz, 2H), 4.34 (br s NH, 1H), 3.96 (t, J = 6 Hz, 1H), 2.16 (s, 3H), 1.98−1.87 (m, 1H), 1.78−1.68 (m, 1H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 146.7, 129.3, 117.7, 112.8, 64.1, 26.1, 24.5, 9.3; HMRS calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1153.

(5) Procedure for Preparation of α-Amino Ketone (10a′). To an aqueous ethanol (5 mL) solution of 2-bromopentan-3-one[18] (500 mg, 3.03 mmol) were added aniline (338 mg, 3.63 mmol), sodium bicarbonate (305 mg, 3.63 mmol), and water (65 mg, 3.63 mmol), and the reaction mixture was heated at 80 °C for 9 h. The solvent was evaporated, extracted with diethyl ether, dried over $MgSO_4$, concentrated, and chromatographed through a silica column to give 2-phenylaminopentan-3-one (**10a′**) as a yellow oil (441 mg, 2.49 mmol, 82%): IR (neat, cm^{-1}) 3416(s), 3047(w), 1721(s), 1614-(w), 1569(s), 1378(s), 1145(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, J = 7.6 Hz, 2H), 6.69 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 7.6 Hz, 2H), 4.34 (br s, NH, 1H), 4.07 (q, J = 6.8 Hz, 1H), 2.58−2.47 (m, 2H), 1.38 (d, J = 7.2 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 146.4, 129.3, 117.8, 112.9, 57.8, 31.5, 18.1, 7.5; HMRS calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1153.

Procedure for Preparation of α-Carbonyl Amide (10b). To a toluene solution (0.80 mL) of hexanamide (**8b**) (85 mg, 0.74 mmol) were added 1-(4-methoxyphenyl)prop-2-yn-1-ol (**3i**) (100 mg, 0.61 mmol), zinc triflate (22 mg, 0.06 mmol), and $TpRuPPh_3(CH_3CN)_2PF_6$ (47 mg, 0.06 mmol), and the reaction mixture was heated at 100 °C for 5 h. The solution was filtered over a short silica bed, washed with diethyl ether (5 mL), and concentrated to give 4-methyl-2,5-diphenyloxazole (**10b**) as a yellow oil (109 mg, 0.39 mmol, 64%): IR (neat, cm^{-1}) 3419 (s), 3048 (w), 3001 (s), 1718 (s), 1676 (s), 1617 (w), 1568 (s), 1452 (s), 1376 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 8.4, 2.0 Hz, 2H), 6.85 (dd, J = 8.4, 2.0 Hz, 2H), 6.71 (d, J = 6.0 Hz, 1H), 5.47 (d, J = 5.4 Hz, 1H), 3.76 (s, 3H), 2.16 (t, J = 6.8 Hz, 2H), 2.07 (s, 3H), 1.60 ∼ 1.52 (m, 2H), 1.30−1.20 (m, 4H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 172.3, 159.7, 129.1, 128.5, 114.5, 62.6, 55.2, 36.3, 31.3, 27.0, 25.1, 22.3, 13.8; HMRS calcd for $C_{16}H_{23}NO_2$ 277.1678, found 277.1679.

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Supporting Information Available: Spectral data for compounds **3a**,**c**,**e**−**i**, **4b**−**i**, **7b**−**f**, **9b**−**g**, NOE map of **4a**,**b**, **7a**,**b**, and X-ray data for compounds **4h** and **9c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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