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Control of 6-*Exo* and 7-*Endo* Cyclizations of Alkynylamides using Platinum and Bismuth Catalysts

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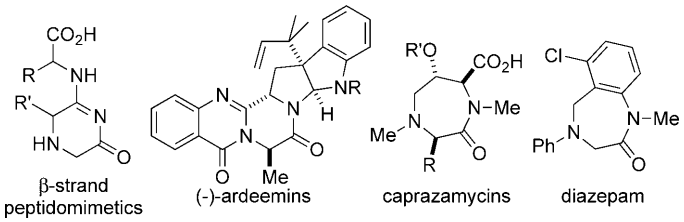
Piperazin-2-one and 1,4-diazepan-2-one scaffolds are featured in biologically active natural products and pharmaceutical compounds,[1] such as peptidomimetics,[2] compounds with potential to reverse multi-drug resistance in cancer treatments (ardeemins),[3] antibiotics (caprazamicins),[4] sedatives, and tranquilizers (diazepam)[5] . These



structures have therefore attracted considerable attention as important pharmacophores in the field of drug discovery. Diverse synthetic methods have been developed for the construction of these *N*-heterocyclic structures, by means of lactamization, the Mitsunobu reaction, reductive amination, and Ugi reactions.[6,7] While piperazin-2-ones are homologous with 1,4-diazepan-2-ones, however, to date no reports on the synthesis of both motifs from the same compound have been reported. To establish a simple and unified method to generate these constructs, we investigated the Lewis acid catalyzed heteroannulation of 2-(prop-2-ynylamino)-acetamide. While there are a number of reports on the 5-*exo*-dig/6-*endo*-dig cyclization of this precursor,[8] there are relatively few reporting the control of the competitive 6-*exo*-dig/7-*endo*-dig cyclization.[9] To our knowledge, the hydroamidation of terminal alkynes has never been described for the synthesis of 1,4-diazepan-2-one and piperazin-2-one with control of diastereoselectivity.[10] The palladium- and gold-catalyzed cyclization of substituted alkynylamides has been reported by our research group and several other groups.[11,12] However, these conditions have not previously been applied to terminal alkynes. Herein, we report the development of highly selective syntheses of 1,4-diazepan-2-ones or piperazin-2-ones by an intramolecular hydroamidation of 2-(prop-2-ynylamino)acetamides, in which regioselectivity is dependent on the Lewis acid catalyst employed.

Initially, we investigated the cyclization of *N*-Ns alkynylamide (Ns = *o*-nitrobenzenesulfonyl (nosyl)) **1a** with different catalytic systems in 1,2-dichloroethane (DCE) at 70 °C and at room temperature (Table 1). A catalyst screening revealed that the 6-*exo*-dig *N*-cyclized product **2a** and the 7-*endo*-dig *N*-cyclized product **3a** were produced in different ratios depending on the Lewis acids used.[13] Surprisingly, when $PtCl_2$ was used as a catalyst,[14] **3a** was obtained in 67% yield with only trace quantities of **2a** generated (Table 1, entry 1). In contrast, the reaction using $PtCl_4$ gave **2a** as the major product (entry 2). Other platinum catalytic systems tested were not effective at promoting cyclization (entries 3 and 4). When a cationic gold catalyst[15] was employed, **3a** was also the major product but lower regioselectivity was obtained compared to that of $PtCl_2$ (entry 5). By using $AgNTf_2$ as a (Tf = CF_3SO_2) catalyst resulted in low reactivity and selectivity, and by-products were observed (entry 6). $[Pd(PhCN)_2Cl_2]$[16] did not promote conversion to the cyclized products at room temperature and only degradation products were observed upon heating (entry 7).

When metals considered to be borderline according to the hard and soft acids and bases (HSAB) principle,[17] such as CuI, $Cu(OTf)_2$, or $In(OTf)_3$ were employed, the starting material was recovered in over 80% yield (Table 1, entries 8–10). In sharp contrast, the reaction with $Bi(OTf)_3$[18] proceeded slowly at room temperature, and afforded the 6-*exo*-cyclized product **2a** as a single product in 75% yield

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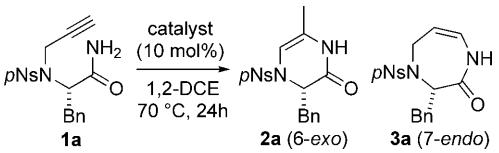
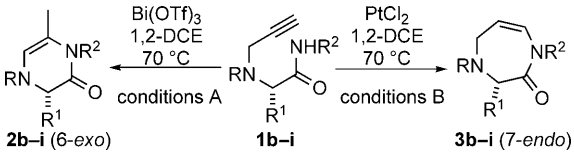
Table 1. Screening of Lewis acid catalysts for the hydroamidation of substrate **1a**.[a]

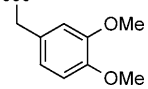
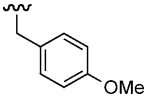
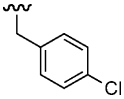


Entry	Catalyst	Yield [%][b]		
		2a	**3a**	SMR[c]
1	$PtCl_2$	1	67	–
2[d]	$PtCl_4$	48	15	–
3	$Pt(cod)Cl_2$	–	trace	99
4[d]	$Pt(cod)Cl_2$, $AgNTf_2$	–	–	–[e]
5[d]	$AuP[(o\text{-biPh})(t\text{Bu})_2]NTf_2$	20	59	–
6	$AgNTf_2$	12	8	27
7	$Pd(PhCN)_2Cl_2$	–	–	–[e]
8	CuI	–	–	99
9	$Cu(OTf)_2$	7	–	82
10	$In(OTf)_3$	17	–	80
11[d]	$Bi(OTf)_3$	75	–	
12	$Bi(OTf)_3$	81	–	–

[a] Ns = nitrobenzenesulfonyl, Bn = benzyl, Tf = trifluoromethanesulfonyl, cod = cyclooctadiene, o-biPh = *ortho*-biphenyl, DCE = dichloroethane. [b] Isolated yield. [c] SMR = starting material recovered. [d] Reaction performed at room temperature instead of 70 °C. [e] Decomposition.

Table 2. Investigation of selective 6-*exo*-dig/7-*endo*-dig hydroamidation of substrates **1b–k**.[a,b]



Entry	Starting Material				Conditions A[a]		Conditions B[a]	
		R	R^1	R^2		Yield [%][c]		Yield [%][c]
1	**1b**	*p*Ns		H	**2b**	82%	**3b**	70%
2	**1c**	*p*Ns		H	**2c**	80%	**3c**	62%
3	**1d**	*p*Ns		H	**2d**	73%	**3d**	59%
4	**1e**	*p*Ns	CH_2OBn	H	**2e**	67%	**3e**	62%
5	**1f**	*p*Ns	*i*Bu	H	**2f**	63%	**3f**	64%
6	**1g**	*p*Ns	*i*Pr	H	**2g**	81%[d]	**3g**	45%[e]
7	**1h**	*p*Ns	Me	H	**2h**	89%[f]	**3h**	0%
8	**1i**	Ts	Bn	H	**2i**	84%	**3i**	73%
9	**1j**	Cbz	Bn	H	**2j**	46%[d]	**3j**	47%
10	**1k**	*p*Ns	Bn	Bn	**2k**	41%[f]	**3k**	40%
11	**1l**	*p*Ns	Bn	*i*Bu	**2l**	43%[f]	**3l**	70%

[a] Conditions A: $Bi(OTf)_3$ (10–30 mol%), 1,2-dichloroethane, 70 °C, 24 h. Conditions B: $PtCl_2$ (10 mol%), 1,2-dichloroethane, 70 °C, 24 h. [b] *i*Bu = isobutyl, *i*Pr = isopropyl, Ts = *p*-toluenesulfonyl, Cbz = benzyloxycarbonyl. [c] isolated yield. [d] H_2O (5 equiv) was added. [e] 6-*Exo*-cyclized product **2g** was obtained in 32% yield. [f] TfOH (10 mol%) was added.

(entry 11). It is noteworthy that $Bi(OTf)_3$ resulted in the opposite regioselectivity to that of $PtCl_2$. By heating at 70 °C, the reaction reached completion to give piperazin-2-one **2a** in 81% yield (entry 12). The 6-*exo*-dig/7-*endo*-dig cyclization could therefore be controlled simply by choice of catalyst.[19]

Our attention was next directed toward the exploration of the substrate scope of the hydroamidation. 2-(Prop-2-ynylamino)acetamides **1b–l** were treated with $PtCl_2$ or $Bi(OTf)_3$ at 70 °C. Representative results are shown in Table 2. First we tested various substitutions at the amide α-position (R^1). The bismuth-catalyzed reaction proved to be less sensitive to R^1 substitution, as various amino acid derivatives **1b–h** converted into piperazine-2-ones **2b–h** in yields of 63 to 89% (Table 2, entries 1–7, conditions A). A benzyl group could be employed for the protection of an alcohol in **1e** (entry 4, conditions A).

Interestingly, 6-*exo* cyclization was not observed in the case of a glycine derivative (R^1 = H, not shown). The platinum-catalyzed cyclizations of L-DOPA derivative **1b** (R^1 = $CH_2(3,4\text{-}(MeO)_2C_6H_3)$), methyl tyrosine derivative **1c**, chlorophenylalanine derivative **1d**, serine derivative **1e**, and leucine derivative **1f** (R^1 = *i*Bu) showed comparable reactivities to the phenylalanine derivative **1a** (entries 1–5, conditions B). On the other hand, treatment of valine derivative **1g** (R^1 = *i*Pr) with $PtCl_2$ gave the 7-*endo*-cyclized product **3g** as well as significant quantities of the 6-*exo*-cyclized product **2g** (entry 6, conditions B). Alanine derivative **1h** did not cyclize under the standard conditions (entry 7, conditions B). These results indicate that a bulky R^1 group is required in the platinum-catalyzed cyclization. *para*-Tosyl or benzyloxycarbonyl (Cbz) groups could be employed instead of a *para*-nosyl group in both cyclizations (entries 8 and 9, conditions A and B). The steric bulk of the substituents on the amide affected the yield. When secondary amides **1k** and **1l** were employed, moderate to good yields were obtained (entries 10 and 11, conditions A and B). It should be noted that in a few cases of the bismuth-catalyzed cyclization, the addition of five equivalents of water or catalytic amounts of trifluoromethanesulfonic acid (TfOH) gave better yields as well as complete conversion (entries 6, 7, and 9–11, conditions A).[20,21] Based on these results, both cyclizations displayed excellent regioselectivity and either piperazin-2-ones or 1,4-diazepan-2-ones could be readily obtained from the same substrates, **1a–f** and **1i–l**.

Proposed mechanisms for each cyclization are presented in Scheme 1. Initially, π activation of the triple bond occurs in both catalytic processes to produce intermediate **4**. Both 6-*exo*-dig and 7-*endo*-dig ring-closing modes are favored by Baldwin's rules.[22] In the case of 6-*exo* cyclization, nucleophilic addition of the amide to the internal carbon triple bond is thought to occur to form intermediate **5**. Subsequent protodemetalation followed by isomerization of the exocyclic double bond to the endocyclic position gives the observed product **2**. The addition of H_2O or TfOH could promote protodemetalation, thereby yielding the desired products in better yields than in the absence of an additive.[21] On the other hand, two possible reaction pathways can be envisioned for 7-*endo* cyclization. The π-activated alkyne **4**

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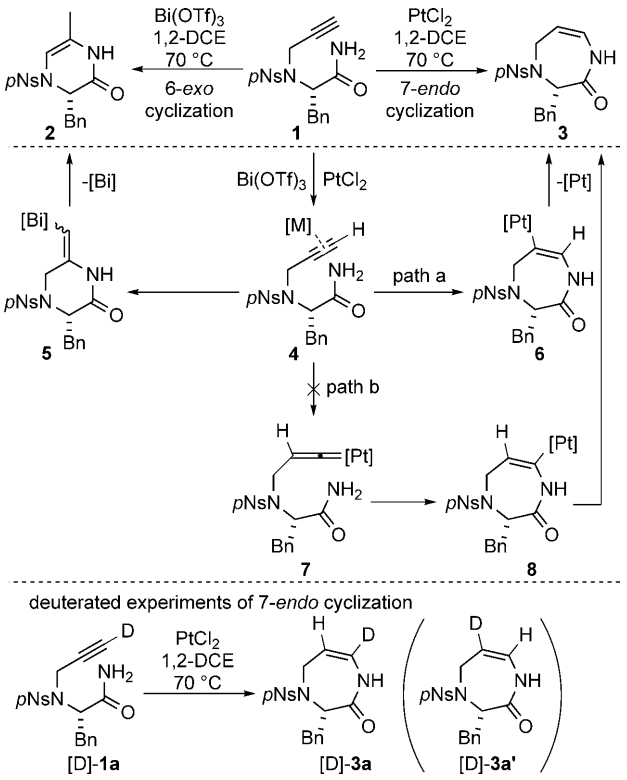

Scheme 1. Deuterated experiment and plausible mechanism.

might cyclize directly to give intermediate **6** (path a). Alternatively, the metal-vinylidene species **7** could form in situ from **4**, and then cyclize into intermediate **8** (path b).[14,23] To differentiate between the above two scenarios, we conducted a deuterium-labeled experiment. The 7-*endo* cyclization of deuterated terminal alkyne [D]-**1a** using $PtCl_2$ afforded the deuterated product [D]-**3a**, while [D]-**3a′** was not observed. This result indicates that path a was preferred to path b in the reaction of **1**. This 7-*endo*-dig ring-closing method affords 1,4-diazepan-2-one **3** after subsequent protonation of metalated intermediate **6**.

In summary, we have developed a simple route to piperazin-2-one and 1,4-diazepanone derivatives through a novel metal-catalyzed intramolecular hydroamidation of terminal and aryl alkynes using $PtCl_2$ and $Bi(OTf)_3$. This atom economical approach requires only a catalytic amount of the appropriate metal complex and selectively provides two different *N*-heterocycles from the same substrate. This method therefore has considerable potential as a route towards two important heterocyclic motifs. Further studies to disclose the reaction scope and gain a deeper insight into the reaction mechanism are currently underway and will be reported in due course.

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Keywords: bismuth · cyclization · heterocycles · piperazin-2-one · platinum

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