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Aminoindolines versus Quinolines: Mechanistic Insights into the Reaction between 2-Aminobenzaldehydes and Terminal Alkynes in the Presence of Metals and Secondary Amines

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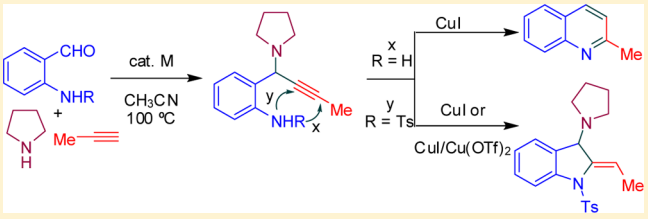
Supporting Information

ABSTRACT: DFT computational studies in the cyclization of aminoalkyne (see structure), which is generated in situ by 2-aminobenzaldehydes and terminal alkynes in the presence of metals and secondary amines, has been investigated. The study revealed that the mode of cyclization (*exo* vs *endo*) depends on the protecting group on nitrogen, the oxidation state of copper, and substitution on alkyne.



INTRODUCTION

In the past few years, the area of π-acid catalysis has emerged as a powerful technique in synthetic organic chemistry.[1] Metals such as Pt, Cu, Ag, and especially Au are the most widely used π-acid catalysts for the activation of C−C multiple bonds.[2] An examination of the literature revealed a plethora of reports involving π-acid-catalyzed cascade reactions.[1] Although some vinylmetal, especially vinylgold, intermediates have been isolated[3] and characterized,[4] very few reports exist on the deep understanding of the mechanism of reactions by computational studies.[5] One of the aspects which needs to be studied in greater detail is the factors that control the *exo*/*endo* selectivity[6] in the activation of alkynes.[7]

As a part of our ongoing interest in the development of π-acid-catalyzed reactions,[8] we recently reported a cooperative catalytic system consisting of metal salts and secondary amines for the synthesis of 2-substituted quinolines (Figure1).[9] A variety of metal salts such as CuLn, $CuLn_2$, AgLn, and AuLn are found to catalyze this transformation, out of which the former one (CuLn) was considered for optimization because of its affordability. Mechanistically, it was proposed that 2-aminobenzaldehyde **1** condenses with the pyrrolidine to give an iminium ion **4**. The iminium ion **4** on reaction with CuI and terminal alkynes **2** would produce intermediates **5** with expulsion of water. A union of copper acetylide and iminium ion, in **5**, would then lead to the formation of copper-coordinated propargylamine derivatives **6**.[10] The intermediates **6** after undergoing 6-*endo*-*dig* cyclization forms **7**. A protonation and aromatization would then occur to give **3** with the liberation of CuI and pyrrolidine. The key feature in the mechanism could be the 6-*endo*-*dig* cyclization in **6** which leads to formation of quinolines (Scheme 1, path a); the undesired 5-*exo*-dig cyclization could result in the formation of aminoindolines **8**.

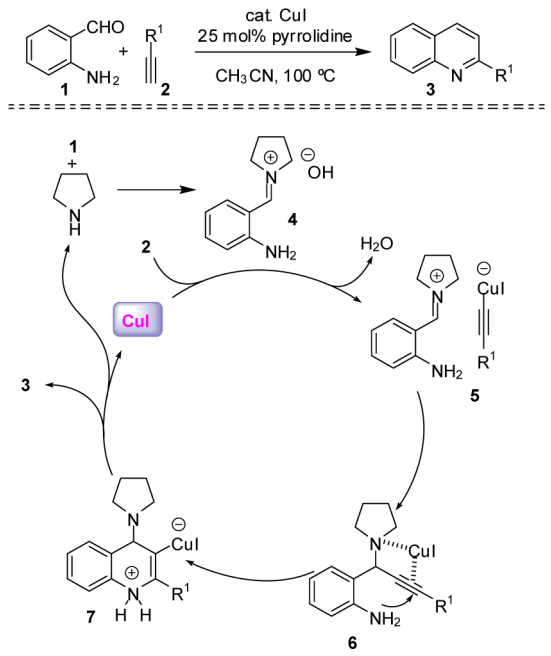


Figure 1. Previously proposed mechanism.

On the contrary, we came across a report from the Gevorgyan's research group wherein they reported a method that involves the reaction between 2-aminobenzaldehydes, secondary amines, and terminal alkynes leading to 3-aminoindolines under the binary catalytic system comprising Cu(I) and Cu(II) catalysts in the presence of DMAP (Scheme 1, path b, Z = NTs).[11] Similarly, there exists a conceptually analogous

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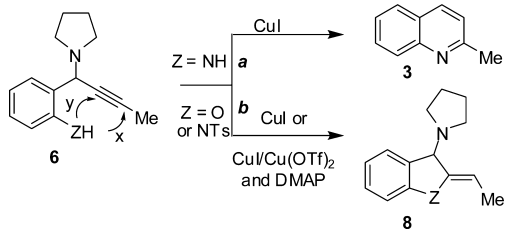
Scheme 1. Product Divergency through *endo*/*exo*-Cyclization



report from Sakai's laboratory which involves the process for the synthesis of benzofurans in good yields (Scheme 1, path b, Z = O).[12]

The main mechanistic feature distinguishing our report[9] from Gevorgyan's[11] and Sakai's[12] reports is the fate of cyclization of in situ generated propargyl amines with tethered nucleophiles. We ask what is the basis for *endo* vs *exo* selectivity: The presence of protecting groups? The nature of the tethered nucleophiles? The effect of catalyst or the presence of DMAP? The observed divergent reactivity between our work and the work of others and the lack of predictability of cyclization of γ-amino alkyne in general encouraged us to explore the subject in detail. Herein, we report a computational study on the mechanism of cyclization of **6**, which is generated in situ by the reaction between 2-aminobenzaldehydes and terminal alkynes in the presence of metals and secondary amines.

RESULTS AND DISCUSSION

Computational Methods. All the geometry optimizations were carried out by using the density functional theory (DFT) method using the Becke's three-parameter exchange functional with the Lee–Yang–Parr correlation functional (B3LYP) level of theory.[13] We have employed a triple-ζ basis set, 6-311+g(d,p), for modeling the main group elements and a relativistic 19-electron shape-consistent LANL2DZ basis set for representing the Cu and I atoms for all of the calculations without the protecting group.[14] For larger molecular systems, we used 6-31+G(d)/LANL2DZ(Cu, I) basis sets. This level of theory has been successful in predicting the mechanisms of the reactions catalyzed by the nanoparticles and complexes of Cu and Au.[15] Frequency calculations were carried out at the same level of theory to ensure that the structure found is a minimum or a transition state. All of the thermochemical energy calculations were done at 298 K. Single-point energies in the solvent acetonitrile were computed by using the B3LYP/6-311+g(d,p)/LANL2DZ(Cu, I) level of theory. The polarizable continuum model with a UAKS (united atom topological model) radius was used.[16] Basis set superposition errors (BSSE) were corrected using the counterpoise correction scheme (see the Supporting Information for the BSSE corrected values in detail).[17] All of the structural calculations were carried out using the G03 suite of programs.[18] The noncovalent interactions were plotted using the NCI plot.[19]

Since the mode of cyclization (*endo* vs *exo*) in **6** is crucial for obtaining the quinolines **3** and indolines **8**, we have computed the energetics for both of the pathways in the presence of the CuI catalyst and pyrrolidine base. The aminoalkyne **9** was considered as a model substrate for performing computational studies (Figure 2). In order to understand the cooperative action of pyrrolidine base with CuI, we modeled the potential energy surface (PES) in its absence also. The reaction mechanisms envisioned for the CuI-catalyzed cycloisomerization pathways in the absence of pyrrolidine base are presented in Figure 2. The Cu catalyst binds with the C–C triple bond of **9** with an exergonicity of ΔG = −19.5 kcal/mol. The BSSE-corrected binding energy of **10** is calculated as $\Delta E_{BSSE} = E(\mathbf{10}) - E(\mathbf{9}) - E(\mathrm{CuI})$ = −23.5 kcal/mol. In the Cu···propargylamine complex **10**, Cu binds symmetrically to the π-bond with the C–Cu bond lengths of 2.12 and 2.13 Å. In a recent paper, Yamamoto et al. have shown that symmetric binding of the

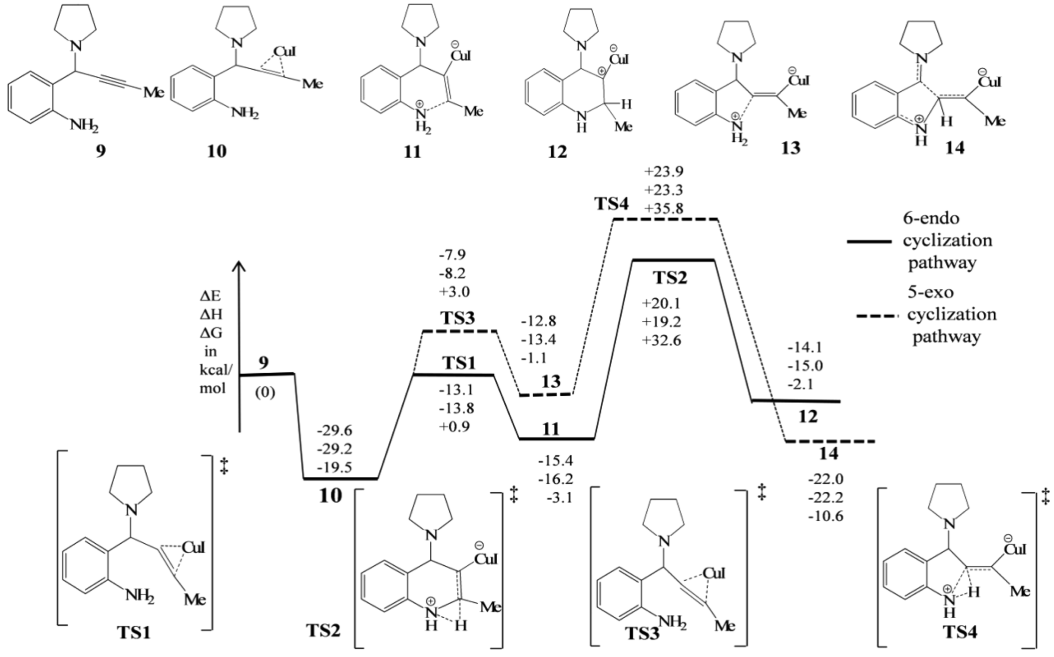


Figure 2. Potential energy surfaces computed for the 6-*endo*-*dig* and the 5-*exo*-*dig* cycloisomerization mechanisms from **9**. The relative energies are given in kcal/mol.

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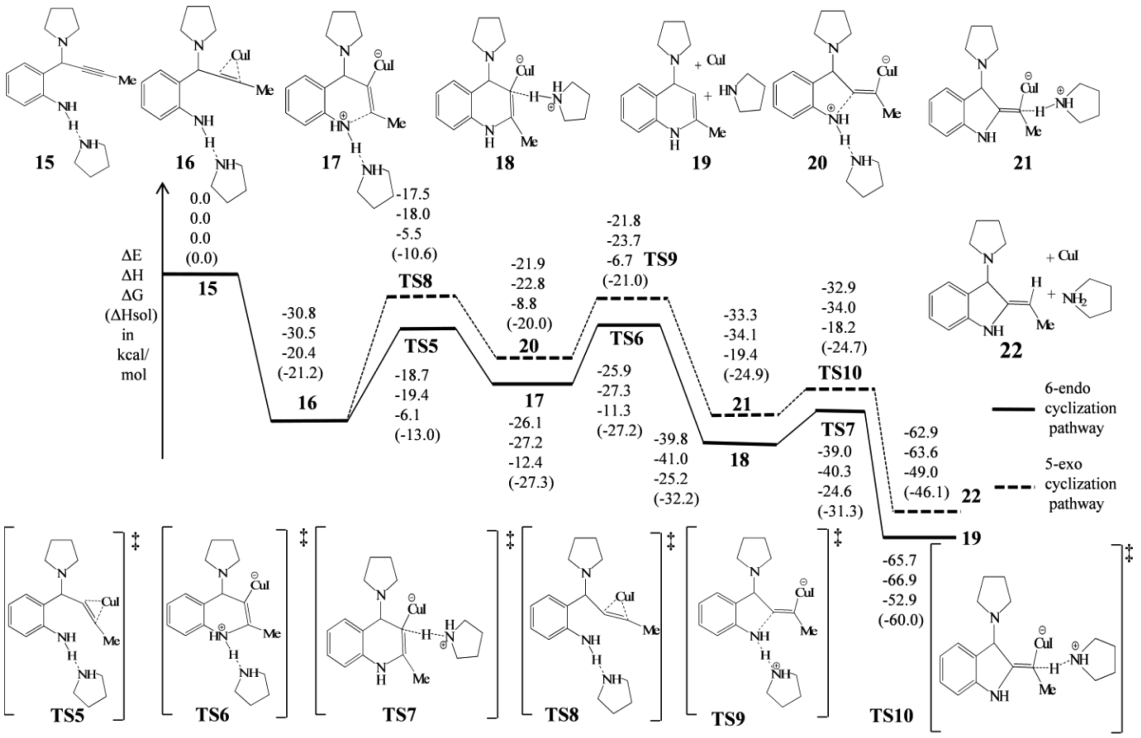

Figure 3. PES envisioned for the mechanisms of cooperative catalysis in the 6-*endo-dig* and 5-*exo-dig* cycloisomerizations of **15**. The relative energies are given in kcal/mol.

catalyst with the π bonds of diaryl acetylenes prefers the formation a 6-*endo* cyclization product.[5a]

The first step in the mechanism would be the attack of nitrogen on the bent alkyne **10**, which is formed by coordination with Cu(I). The next step would be a 1,2-proton shift from the amine nitrogen to the nearest carbon of the corresponding cyclized intermediate, **11** or **13**. In the subsequent steps, *ipso*-protodemetalation from the intermediates **12** or **14** leads to the product···Cu complex. The activation energy for the angle-closure TS (**TS1**) for the 6-*endo-dig* cyclization is calculated as $\Delta G^{\ddagger}$ = 20.4 kcal/mol and the formation of the intermediate **11** is endergonic by ΔG = 16.4 kcal/mol. The crossing of the barrier-**TS2** for a subsequent 1,2-proton shift from the NH_2 group of **11** requires an activation energy of $\Delta G^{\ddagger}$ = 35.7 kcal/mol. The intermediate Cu···complex thus formed (**12**) can facilitate the formation a quinoline···Cu complex from an *ipso*-protodemetalation process. An alternative 5-*exo-dig* cycloisomerization pathway starting from the CuI−alkynophilic complex was also modeled and compared with the 6-*endo-dig* cyclization. The bending of the π-bond in **10** in a 5-*exo-dig* fashion is more energy demanding than the 6-*endo-dig* cyclization ($\Delta G^{\ddagger}$ = 22.5 kcal/mol versus 20.4 kcal/mol for **TS3** and **TS1**, respectively). Also, the 1,2-proton shift from the NH_2 group of 5-*exo*-cyclized intermediate requires crossing of a higher energy barrier-**TS4** of $\Delta G^{\ddagger}$ = 36.9 kcal/mol. The above findings favor the 6-*endo* cyclization of **10** in the presence of CuI over the 5-*exo-dig* cyclization. However, the energy requirement for the 1,2-proton shift is very high in both cases. In a recent paper, we have shown that the Au(III)-catalyzed cycloisomerization of allenone is catalytically assisted by the protonating agent $CF_3CO_2^-$ through a fast protodemetalation step instead of 1,2-proton shifts.[15a] Since, similar counterion/solvent assisted cycloisomerizations have been reported in literature,[20] we further looked the involvement of cocatalytic activity of the protonating agent, i.e., pyrrolidine, used in the experiments.

Cooperative Catalysis by Pyrrolidine Base and CuI. As shown in Figure 3, the amine moiety of **9** binds with the pyrrolidine through a N−H···N hydrogen bond of length 2.16 Å (cf. **15**). The BSSE-corrected binding energy of **15** with respect to **9** and pyrrolidine is calculated as ΔE_{BSSE} = −3.71 kcal/mol. The catalyst CuI binds with the triple bond of **15** to form the π-philic complex **16**. The interaction energy of Cu to **15** is ΔE_{BSSE} = −23.5 kcal/mol. In structure **16**, the binding of CuI to the π bond remains symmetric.

The potential energy surfaces (PES) for both the 6-*endo-dig* and the 5-*exo-dig* cyclization modes of propargylamine derivative **9** in the presence of CuI and pyrrolidine are envisioned. Our computation reveals that the 6-*endo-dig* cyclization is both thermodynamically and kinetically favorable over the 5-*exo-dig* cyclization. The barrier for 6-*endo* cyclization, **TS5** ($\Delta G^{\ddagger}$ = 14.3 kcal/mol), is less energy demanding than the barrier for 5-*exo* cyclization, **TS8** ($\Delta G^{\ddagger}$ = 14.9 kcal/mol), by 0.6 kcal/mol. Single-point energies, calculated in the solvent acetonitrile with the gas-phase optimized geometries, shows inconsistent relative free energies due to the presence of small imaginary frequencies (<20 cm^{-1}). However, the relative changes in the enthalpy remain consistent. Hence, the ΔH_{sol} values are reported. Solvent calculations favor the **TS5** over **TS8** by $\Delta\Delta H^{\ddagger}_{sol}$ = 2.4 kcal/mol. In addition, the 6-*endo-dig* cyclized intermediate (**17**) is more stable than the 5-*exo-dig* cyclized intermediate (**20**) by $\Delta\Delta G^{\ddagger}$ = 3.6 kcal/mol ($\Delta\Delta H_{sol}$ = 16.0 kcal/mol in acetonitrile). It shows that the 6-*endo-dig* cyclization transition state and the intermediate are more stabilized in the implicit solvation model used. Interestingly, in all these mechanisms, the barriers for cyclization have reduced considerably than the respective barriers computed in the absence of a pyrrolidine. The newly formed C−N bonds in **17**

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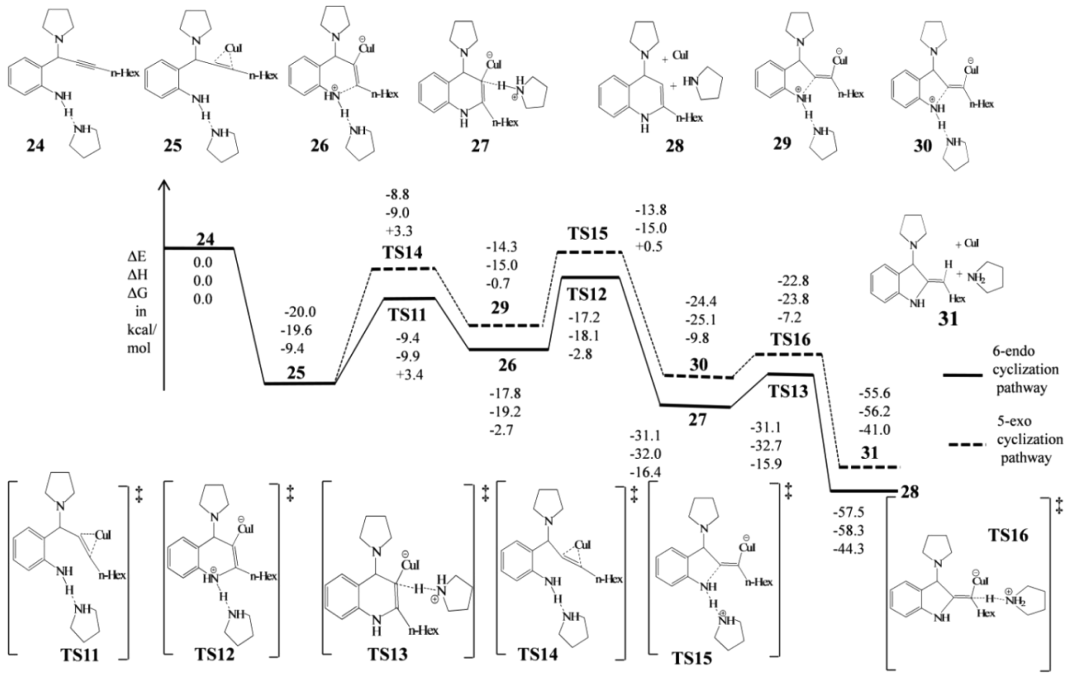

Figure 4. PES envisioned for the mechanisms of cooperative catalysis in the 6-*endo-dig* and 5-*exo-dig* cycloisomerizations of **24**. The relative energies are given in kcal/mol.

and **20** (bond distances are of 1.53 and 1.56 Å, respectively) are longer than the usual C−N σ bonds (∼1.47 Å). In the cyclized intermediates **17** and **20**, the N−H···N hydrogen bond lengths (= 1.74 Å and 1.75 Å, respectively) are shortened and N−H···N bond angles (= 173.9° and 168.6°, respectively) are increased considerably. It favors a very facile hydrogen abstraction by the pyrrolidine in the subsequent step. Barriers for the proton abstractions by pyrrolidine from **17** (through **TS6**) and **20** (through **TS9**) are of just 1.1 and 2.1 kcal/mol, respectively, compared to 35.7 kcal/mol (**TS2**) and 36.9 kcal/mol (**TS4**) for the respective 1,2-H-shift mechanisms in the absence of pyrrolidine. It explains the cooperative catalysis by pyrrolidine found in the experiments. In the subsequent cascades, the protonated pyrrolidine base promotes the protodemetalation steps through the small barriers of $\Delta G^{\ddagger}$ = 0.6 kcal/mol (**TS7**) and 1.2 kcal/mol (**TS10**) in the PES of 6-*endo-dig* and 5-*exo-dig* cycloisomerization paths. The CuI···quinoline complex **19** on reaction with **9** would regenerate the product **23** and the π-philic Cu complex **16**. The exergonicity for this reaction is of −2.0 kcal/mol.

In order to further confirm the proposed mechanisms, we explored other possibilities for the 6-*endo-dig* cyclization. In the lowest energy mechanism shown in Figure 3, both of the pyrrolidine rings in **TS5** and **TS8** are on the opposite faces. However, an alternate mechanism is possible in which both the pyrrolidine rings come on the same face in the angle closure TS (see Figure S1, Supporting Information). This PES has a higher energy requirement for the 6-*endo* bending mode. The solvent state calculations and subsequent proton rearrangement mechanisms do not change this preference for the proposed mechanism envisioned in the Figure 3.

Next, we computed the PES for the cycloisomerization modes with *n*-hex substituent on the C−C triple bond. The PES modeled for the cycloisomerization of hexyl-substituted propargylamine derivative is shown in Figure 4. The interaction energy of Cu complex **25** is ΔE = −20.0 kcal/mol. The Cu catalyst binds with **25** symmetrically with the C−Cu bond lengths of 2.13 and 2.14 Å as in **16**. Hence, we predict that the electron-donating group *n*-hex do not change the chemoselectivity of the reaction. The energetics computed for the barriers and intermediates confirms the preferences for the 6-*endo*-cyclization modes. The 6-*endo*-cyclized intermediate **26** is more stable than the 5-*exo*-cyclized intermediate **29** by ΔG = 2 kcal/mol. This thermodynamic preference for the 6-*endo* cyclization is conserved throughout the PES. Thus, the intermediates **27** and **28** are more stable than 5-*exo*-cyclized species **30** and **31**, respectively. Along with this, energetically favorable barriers confirm that the 6-*endo-dig* cyclization mechanism is both kinetically and thermodynamically more favorable than the 5-*exo-dig* cycloisomerization. An alternative, more energy demanding 6-*endo-dig* cycloisomerization mechanism was also computed in which the two pyrrolidine rings in **24** do approach in the same face of the angle closure TS (see Figure S2, Supporting Information, for a detailed mechanism).

Effect of Protecting Group and the Oxidation State of the Catalyst. The major differences from the synthetic strategy of Gevorgyan's group (Scheme 1, path b, Z = NTs) from our reported reaction (Scheme 1, path a, Z = NH) are of (1) the presence of protecting group −Ts and (2) the combination of Cu(I)/Cu(II) catalysts. Therefore, an understanding of the effect of the −Ts group and the oxidation states of the catalyst in the reaction mechanism is highly desirable. 4-Aminopyridine ($H_2NC_5H_4N$) and the sulfonyl phenyl ($-C_6H_4SO_2$) group were used as the model systems for studying the effects of 4-dimethylaminopyridine (DMAP) base and the tosyl (−Ts) protecting group, respectively. As a proof of principle, calculations were performed for the cyclization in the presence of other common amine protecting groups, an amide protecting group (−NHCHO) and a carbamate ($-NHCO_2H$) group. The model designed to study the propargylamine derivatives is presented in Figure 5 and their structural parameters, interaction energies of the Cu catalysts,

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and Mulliken charges on the selected elements are given in Table 1.

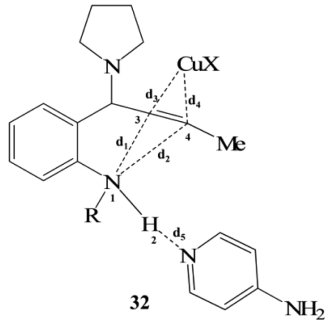

Figure 5. Structure of propargylamine derivatives studied.

We found that the binding energy of Cu decreases when R = Ts. Also, an increase in the interaction energy of $[CuOTf]^+$ compared to CuOTf and CuI is understood from the increased Lewis acid nature of Cu^{2+} compared to that of Cu^+. Substitution of the electron-withdrawing group −Ts decreases the bond distance d_5 between N and H_2 due to the increase in the positive charge density on H_2 (see the Mulliken charges on H_2). The decrease in both the distances d_1 and d_2 on −Ts substitution shows that the nucleophilic attack on the π-bond is more favored with Ts. In **32** without −Ts, the hydrogen atom attached to N_1 is facing the sp carbon C_3 (H−C_3 bond distance of 2.29 Å). Hence, for the 5-*exo* cyclization to occur, the Cu coordinated C−C triple bond has to bend in an energetically unfavorable way. The noncovalent interactions were plotted for **32a** and **32b** (Figure S10, Supporting Information). The NCI plot for R = Ts shows an attractive interaction between C_3 and N_1, which is absent when R = H, since the H-atom positioned between N_1 and C_3 hinders the N_1−C_3 interaction. This, we believe, is the reason for the change in the chemoselectivity in the presence of −Ts despite of the fact that $d_1 < d_2$ in both cases.

The preference for the 5-*exo-dig* cycloisomerization predicted from the ground state geometries were also confirmed through the PESs modeled with −Ts (Figure 6), −CHO, and $-CO_2H$ groups. In the presence of the protecting group −Ts, the barrier for angle closure in 5-*exo-dig* fashion (**TS17**) is $\Delta G^{\ddagger}$ = 14.5 kcal/mol. It is more stable than the 6-*endo-dig* cyclization barrier (**TS18**) by $\Delta\Delta G^{\ddagger}$ = 15.5 kcal/mol. Also, the 5-*exo-dig* cyclization intermediate (**34**) is more stable than **35** by $\Delta\Delta G$ = 31.5 kcal/mol. Hence, the 5-*exo-dig* cycloisomerization in the presence of the −Ts group is both kinetically and thermodynamically favored. The PESs computed for the

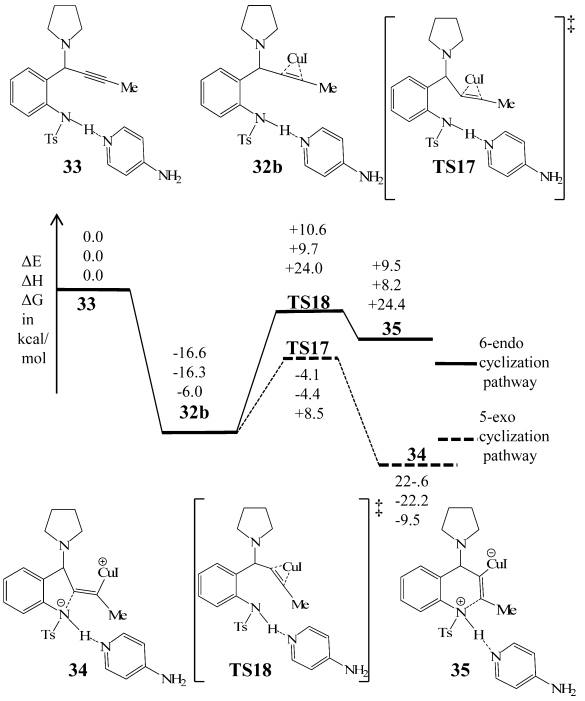

Figure 6. PES computed for the cycloisomerization pathways of **33**. The relative energies are given in kcal/mol.

cyclization modes with an amide protecting group (**32g**) and a carbamate protecting group (**32h**) support the above findings. Our computation shows that the barriers for the 5-*exo-dig* cyclization are less energy demanding than the 6-*endo-dig* cyclization by ΔG = 12.1 and 11.2 kcal/mol in the case of amide and carbamate groups, respectively. Hence, the substitution on amine with the protecting groups controls the selectivity of the cyclization irrespective of the size or steric bulkiness of the substituents modeled. The above results could be applied to explain the 5-*exo-dig* cycloisomerization observed by Sakai et al. We have also modeled the structure **6** (Z = O) hydrogen bonded to DMAPH (see the Supporting Information). There is no hydrogen atom hindering the interaction between the oxygen atom and the π-bond. Hence, the cycloisomerization would proceed in a 5-*exo-dig* manner without the requirements of a protecting group on oxygen as observed in the experiments.

CONCLUSION

In conclusion, the mechanism of reaction between 2-aminobenzaldehydes and terminal alkynes in the presence of metals and secondary amines has been investigated through DFT

Table 1. Binding energies, Bond Distances, and Mulliken Charges on Selected Elements for the Model Systems Used for Study

				selected bond lengths (in Å)					Mulliken charges on elements			
model system	CuX	R	binding energy of CuX (in kcal/mol)	d_1	d_2	d_3	d_4	d_5	N_1	H_2	C_3	C_4
32a	CuI	H	−19.7	3.07	3.64	2.13	2.14	2.09	−0.74	0.48	0.88	0.74
32b	CuI	Ts	−16.6	2.95	3.58	2.12	2.15	1.92	−0.65	0.53	1.13	0.91
32c	CuOTf	H	−38.3	2.97	3.80	2.04	3.31	1.97	−0.99	0.51	1.15	0.71
32d	CuOTf	Ts	−22.6	2.96	3.63	2.06	2.07	1.91	−0.60	0.53	1.66	0.87
32e	$[CuOTf]^+$	H	−99.0	4.30	5.40	2.18	2.04	1.86	−0.84	0.49	0.18	0.32
32f	$[CuOTf]^+$	Ts	−84.6	3.63	4.50	2.09	2.13	1.81	−0.86	0.55	0.73	0.43
32g	CuI	CHO	−18.4	3.00	3.60	2.12	2.14	1.96	−0.33	0.51	1.47	0.94
32h	CuI	CO_2H	−18.6	2.92	3.37	2.13	2.14	1.95	−0.62	0.51	1.03	0.81

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computational studies. The computed mechanism truly confirms the cooperative catalysis between the Cu catalysts and the pyrrolidine. It was found that the presence of a amine-protecting group in the starting material can tune the chemoselectivity of the reactions. Hence, our computations show that in the carbon−heteroatom bond forming cyclization reactions triggered by π-bond activation, one should routinely test the effect of the heteroatom protecting group for switching regioselectivity.[21] We believe that the present study could also help in understanding other cooperative catalytic processes involving other metal catalysts (especially Au and Pt) and secondary amines.[22]

■ ASSOCIATED CONTENT

Supporting Information

Computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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