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Microwave-Assisted Intramolecular Huisgen Cycloaddition of Azido Alkynes Derived from α-Amino Acids

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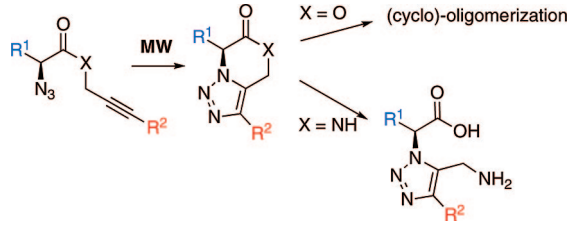


The intramolecular version of the Huisgen cycloaddition is a potentially useful reaction for the stereocontrolled preparation of 1,5-disubstituted and 1,4,5-trisubstiututed triazoles. When α-azido propargyl esters derived from α-amino acids are submitted to [3 + 2] cycloaddition, the expected 4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazin-6-ones are not formed; rather, an oligomeric cyclic polyester is obtained via a prevailing intermolecular cycloaddition. We have discovered that propargyl α-azido amides undergo metal-free intramolecular Huisgen cycloaddition in MeCN/H_2O under microwave dielectric heating. This reaction provides access to new condensed triazoles that can be considered as conformationally constrained peptidomimetics. Moreover, the following microwave-assisted lactam ring opening provides 1,4-disubstituted and 1,4,5-trisubstituted triazole amino acids. The same kind of compounds are obtained from the ester cycloadduct by reaction with primary amines in the presence of $AlMe_3$. In order to interpretate this unpredictable behavior, an ab initio study of the reaction pathway was undertaken using GAMESS(US) at the B3LYP/6-31G** level of theory. Different relaxed potential energy profiles were obtained for esters and amides, suggesting that the *cis*-arrangement of the −CO═N− could account for the amide reactivity.

Introduction

In recent times, azides have became one of the most useful functional groups in organic chemistry.[1] This is due in part to their ability to undergo Cu-catalyzed cycloaddition with terminal alkynes[2] as well as applications in bioorganic[3] and medicinal chemistry.[4] In addition to reacting in high yield and simple product isolation, one of the main features of this reaction is the possibility to control the regiochemistry of the addition providing exclusively 1,4-disubstituted triazoles. Recently, the possibility of using Ru catalysts to produce 1,5-disubstituted triazoles has been described,[5] although this has not been investigated as widely as Cu.[6] Regiocontrol is still an issue when targeting 1,4,5-trisubstituted triazoles.[7] Recently, the regiocontrolled synthesis of 5-aryl, 1,4-trisubstituted 1,2,3-triazoles via a click reaction/direct triazole CH insertion sequence has been reported.[8]

Several authors have recently demonstrated that "click" Cu-catalyzed reactions can be also used as assisted methods for

(1) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.

(2) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51. Gil, M. V.; Arévalo, M. J.; López, O. *Synthesis* **2007**, 1589.

(3) Kolb, H.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. Vocadlo, D. J.; Bertozzi, C. R. *Angew Chem. Int. Ed.* **2004**, *43*, 5338. Sawa, M.; Hsu, T.-L.; Itoh, T.; Sugiyama, M.; Hanson, S. R.; Vogt, P. K.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12371.

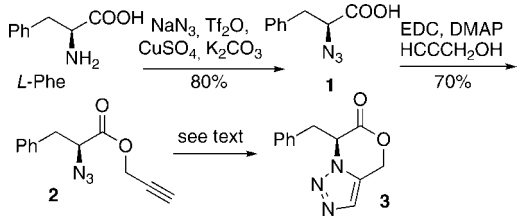
(4) For example, see: (a) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686. (b) Brik, A.; Muldoon, J.; Lin, Y.-C.; Elder, J. H.; Goodsell, D. S.; Olson, A. J.; Fokin, V. V.; Sharpless, B.; Wong, C.-H. *ChemBioChem* **2003**, *4*, 1246. (c) Speers, A. E.; Cravatt, B. F. *Chem. Biol.* **2004**, *11*, 535. (d) Burley, G. A.; Gierlich, J.; Mofid, M. R.; Nir, H.; Tal, S.; Eichen, Y.; Carell, T. *J. Am. Chem. Soc.* **2006**, *128*, 1398.

(5) Zhang, L.; Chen, X.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.

(6) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337. For the synthesis of the catalyst see:Chinn, M. S.; Heinekey, D. M. *J. Am. Chem. Soc.* **1990**, *112*, 5166.

10.1021/jo802463r CCC: $40.75
Published on Web 01/12/2009

SCHEME 1. Reaction of Azide Esters



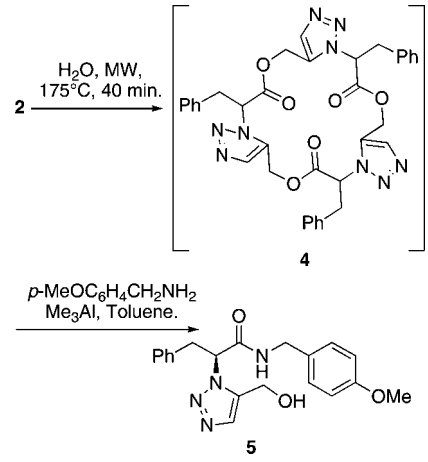
ring closing of macrocyclic (pseudo)-peptides.[9] However, the regiochemical control in the Cu-mediated reaction can be a limitation when the triazole must be inserted in a cycle containing less than 14 atoms, as in the case of triazole containing β-turn mimic peptides.[10] The development of an intramolecular version of the Huisgen cycloaddition (copper free) can be an useful alternative to drive the regiochemistry of the cycloaddition toward the complementary isomer in respect to the product of the Cu mediated reaction. The introduction of a labile template between the azide and the alkyl moieties would allow the further hydrolysis with formation of the expected fully elaborated triazole. With the idea to investigate the possibility of forcing the regiochemistry of the Huisgen cycloaddition through an intramolecular reaction, we decided to choose the ester or the amide function as the labile template suitable of postcycloaddition cleavage.[11]

Results and Discussion

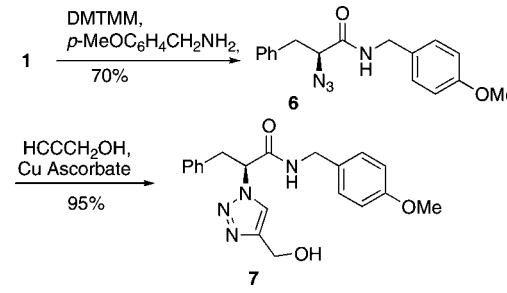
Starting from L-phenylalanine, the corresponding α-azido acid **1** was prepared following a literature report.[12] Further reaction with propargyl alcohol in the presence of EDC and DMAP gave compound **2**, which was employed as the model to find the best reaction conditions for cyclization (Scheme 1).

Based on classical reports on thermal Huisgen cycloaddition,[13] we initially subjected **2** to conditions of refluxing toluene for several hours which gave mainly unreacted starting material. Using microwave dielectric heating and toluene as the solvent, the reaction mixture did not reach a temperature suitable for cyclization. The addition of a catalytic amount of the ionic liquid [bmim][BF_4] to the toluene increased the temperature up to 180 °C without formation of the cycloadduct. When water was employed as the solvent, the formation of a precipitate was observed after heating at 175 °C for 40 min (200 W power, max internal pressure 200 psi). Unfortunately, after separation,

SCHEME 2



SCHEME 3



the precipitate could not be dissolved in any solvents. Diluted NMR spectra in DMSO-d_6 showed the resonances expected for the cyclization product (with a large shape); however, analysis of the ES/MS spectra suggested the formation of oligomers. Product **3** was not formed even with the increase of the dilution (up to 10^{-4} M). With the aim to improve reactivity increasing the solubility of **2**, mixtures of THF/water, acetone/water, EtOH/water, or the corresponding organic solvents alone were tried, but again, **3** was obtained in very low yields.[14] Attempts to use classical "click" conditions (Cu(II) salts and Na ascorbate) or the Cp*$RuCl(PPh_3)_2$ catalyst were unsuccesful, possibly due to the hindrance that the alkyne−metal complex exerts to the rest of the molecule.

In order to prove the effective formation of the oligomers proposed on the basis of the molecular weight deduced from ESI-MS specrum, aminolysis of the ester bond was attempted. Treatment of the presumed oligomer **4** with *p*-methoxybenzylamine and Me_3Al in refluxing toluene resulted in the isolation of triazole **5** in 32% yield (Scheme 2). Compound **5** was the only species containing a triazole ring present in the reaction mixture.[15] In order to ascertain the regiochemistry of **5**, the 1,4 disubstituted derivative **7** was prepared following standard "click" chemistry (Scheme 3).

The comparison between the ^{1}H NMR spectra of **5** and **7** showed substantial differences in the resonances of several protons, suggesting that **5** was the 1,5 isomer.

Changes in the nature of the starting amino acid were also examined, but the corresponding azido esters never cyclized properly to provide oligomers that could be cleaved with amine

(7) For an approach to regioselective intermolecular Huisgen reaction with internal alkynes using the Ru catalyst, see: Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680.

(8) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081.

(9) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145. Turner, R. A.; Oliver, A. G.; Lokey, R. S. *Org. Lett.* **2007**, *9*, 5011. Looper, R. E.; Pizzirani, D.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 2063.

(10) Angell, Y.; Burgess, K. *J. Org. Chem.* **2005**, *70*, 9595.

(11) For examples of intramolecular formation of 1,2,3-triazoles not oriented to the regiocontrolled synthesis of substituted triazoles, see: Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134. Thomas, A. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1881. Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahderon Lett.* **2004**, *45*, 8429. Hotha, S.; Anegundi, R. I.; Natu, A. A. *Tetrahedron Lett.* **2005**, *46*, 4585. Mohapatra, D. K.; Maity, P. K.; Gonnade, R. G.; Chorghade, M. S.; Gurjar, M. K. *Synlett* **2007**, 1893. Oliva, A. I.; Christmann, U.; Font, D.; Cuevas, F.; Ballester, P.; Buschmann, H.; Torrens, A.; Yenes, S.; Pericas, M. A. *Org. Lett,* **2008**, *10*, 1617. Sudhir, V. S.; Baig, R. B. N.; Chandresekaran, S. *Eur. J. Org. Chem.* **2008**, 2423. For one example of intramolecular reaction appied to the synthesis of a triazole amino acid as peptide turn inducers, see: Pokorski, J. K.; Miller Jenkins, L. M.; Feng, H.; Durell, S. R.; Bai, Y.; Appella, D. H. *Org. Lett.* **2007**, *9*, 2381.

(12) Lundquist, J. T., IV.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781.

(13) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604.

(14) In no case did we isolate a discrete product having ^{1}H NMR and MS spectra fully coherent with the proposed structure.

(15) Data recovered by analysis of the mass spectra of all the components of the reaction mixture.

SCHEME 4. Reaction of Azido Amides

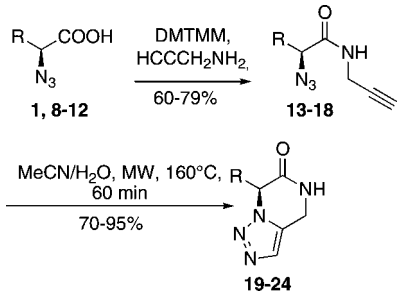


TABLE 1. Cyclization of Amides 13−18

R	amide, yield (%)[a]	triazole, yield (%)[a]
$C_6H_5CH_2$-	**13** (70)	**19** (94)[b]
CH_3-	**14** (65)	**20** (94)[c]
$(CH_3)_2CH$-	**15** (79)	**21** (93)[c]
$(CH_3)_2CHCH_2$-	**16** (75)	**22** (94)[c]
$CH_3SCH_2CH_2$-	**17** (68)	**23** (94)[c]
$BocNH(CH_2)_4$-	**18** (60)	**24** (70)[c]

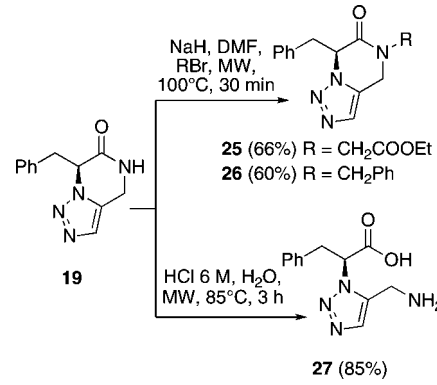
[a] Yields of isolated compounds. [b] 70% ee. [c] >95% ee.

and $AlMe_3$ to produce the 1,5-disubstituted triazoles in yields suitable for preparative purposes.

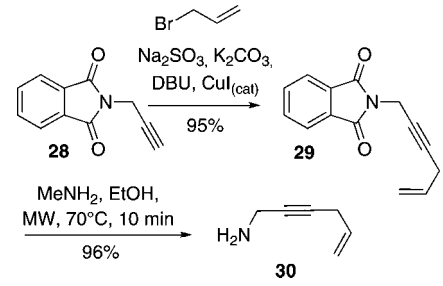
In addition to the investigation on esters, the intramolecular cycloadditon was also attempted on amide **13**, prepared as described in Scheme 4.[16] We were surprised and gratified to find that cycloadduct **19** was obtained in good yield when the reaction was carried out in wet MeCN. [17] Optimization of the procedure ($MeCN/H_2O$ 4:1, 160 °C, maximum internal pressure 200 psi, 60 min) gave **19** in 94% isolated yields after evaporation of the solvent and crystallization.

This reaction condition proved to be effective on other α-azido propargylamides (**14−18**), prepared from the α-amino acids **8−12** as described above. The corresponding 7-substituted-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-ones (**20−24**) were obtained in good yields (Table 1) after simple crystallization from $EtOH/H_2O$. Compounds **20−24** were obtained in ee >95%. Compound **19** was instead obtained with ee = 70%, due to partial racemization of the phenylalanine azide during the prolonged heating.[18] In order to increase the molecular diversity around the newly formed heterocycle, the possibility of further functionalization at the amide NH was explored (Scheme 5). Treatment of **19** with $BrCH_2COOEt$ or BnBr in DMF in the presence of NaH under microwave dielectric heating, gave compounds **25** and **26** in good yields.[19] Alternatively, microwave-assisted hydrolysis of the lactam bond occurred at 85 °C for 3 h in HCl 6 M in water and produced the 1,4-disubstituted triazole amino acid **27** in good yields.[20] This reaction sequence provided an alternative way to prepare disubstituted triazole amino acids regiocomplementary to the isomers obtained through the Cu-mediated reaction.[21]

SCHEME 5



SCHEME 6



In order to apply this procedure to the synthesis of trisubstituted triazoles,[22] propargylamine **30** was prepared. Allylation of *N*-propargylphthalimide **28** occurred rapidly and in good yields under very mild conditions, adapting a procedure previously described for simple alkynes (Scheme 6).[23] We found it convenient to prepare **30** by treatment of **29** with an excess of $MeNH_2$ in EtOH under microwave dielectric heating that provided **30** in higher yield and purity when compared to refluxing conditions (less than 40% of product isolated after 12 h of reflux).

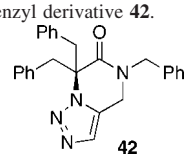
Coupling of amine **30** with α-azido acids **1** and **8−10** in the presence of DMTMM[17] gave α-azido amides **31−34** in good yields. Our first attempts to apply the standard conditions to the cyclization of **31** gave the bicyclic triazole **35** in 30% yield after 1 h of microwave dielectric heating at 160 °C. After two additional cycles of 1 h each, an 80% conversion of **31** into the triazole was effected. Purification by column chromatography gave bicyclic triazole **35** in 65% yields as a single isomer. The

(16) Zhao, H.; Sanda, F.; Matsuda, T. *Macromolecules* **2004**, *37*, 8888. DMTMM: 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride. See: Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 277. DMTMM is commercially available from Acros Organics.

(17) When MeCN alone was used as the solvent, the solution did not reach the temperature required for cycloaddition. When ionic liquid was employed in order to increase the internal temperature, cycoaddition did not occur.

(18) HPLC analysis with Chiral Column Chiralpack 1B 0.46 × 15 cm.

(19) The yields reported in the scheme were obtained exclusively when the vial containing all the reagents was submitted to MW heating. When the classical procedure of succession in reagent addition was followed, very low yields were obtained at room temperature, whereas MW heating (after addition of benzyl bromide) provided the dibenzyl derivative **42**.



(20) Compound **27** was obtained in 70% ee, the same of the starting compound **19.** When lactam hydrolysis was attempted in oil bath at 100 °C, more then 24 h were required to obtain 75% yields of **19**.

(21) For the Cu-catalyzed synthesis of triazole-containing amino acids, see: Angelo, N. G.; Arora, P. S. *J. Am. Chem. Soc.* **2005**, *127*, 17134.

(22) Although it is possible, no applications of intramolecular cycloaddition to the synthesis of trisubstituted triazoles have been reported until now. For one example of the synthesis of substituted bicyclic triazole via ring opening of aziridine-propargylic derivatives, see: (a) Kim, M. S.; Yoon, H. J.; Lee, B. K.; Known, J. H.; Lee, W. K.; Kim, Y.; Ha, H.-J. *Synlett* **2005**, 2187. (b) Yanai, H.; Taguchi, T. *Tetrahedron Lett.* **2005**, *46*, 8639.

(23) Bieber, L. W.; da Silva, M. F. *Tetrahedron Lett.* **2007**, *48*, 7088.

SCHEME 7

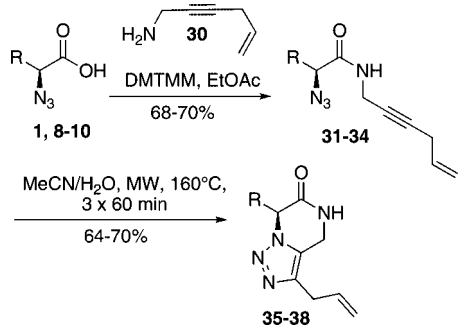
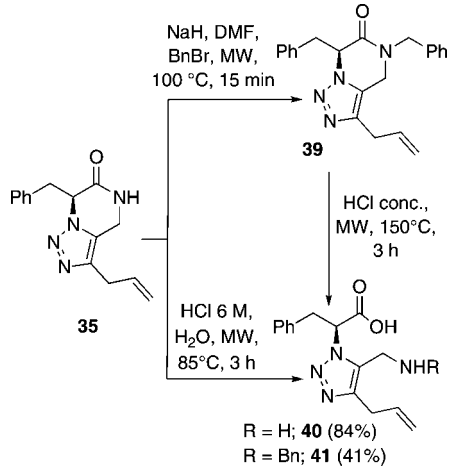


TABLE 2. Cyclization of Amides 31−34

R	amide, yield (%)[a]	triazole, yield (%)[a]
$PhCH_2$-	**31** (70)	**35** (65)[b]
CH_3-	**32** (70)	**36** (64)[c]
$(CH_3)_2CH$-	**33** (68)	**37** (64)[c]
$(CH_3)_2CHCH_2$-	**34** (70)	**38** (70)[c]

[a] Yields of isolated compounds; 5−10% of starting material recovered after column chromatography. [b] 70% ee. [c] >95% ee.

SCHEME 8



time required for cyclization of **31** was remarkably long if compared with standard microwave-assisted reaction.[24]

The use of microwave heating was critical to the success of the reaction. When the cyclization was attempted at the same temperature under conventional heating, after 24 h of stirring the reaction mixture in a sealed vial immersed in an oil bath heated at 160 °C, the starting material was completely consumed without formation of compound **35**. Cyclisation was repeated on amides **32**−**34** giving the expected triazoles **35**−**38** in acceptable yields (Scheme 7 and Table 2).

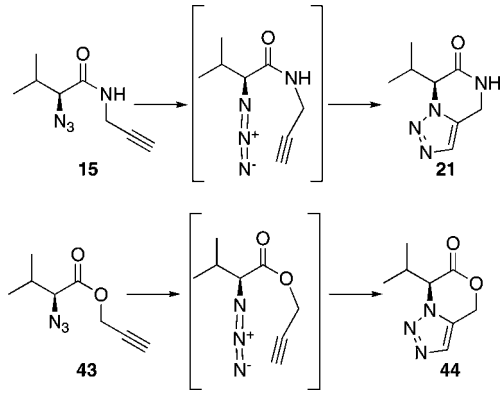
Further elaboration of **35**−**38** by alkylation of the nitrogen, lactam ring opening, or functionalization of the double bond[25] is possible. (Scheme 8).

For example, the *N*-benzyl derivative **39** was obtained by microwave dielectric heating of **35** in the presence of BnBr and Na in DMF. Analogously, the 1,4,5-trisubstituted amino acids **40** and **41** were obtained after microwave-assisted lactam

(24) Comparable yields were observed by heating in succession of 20 min irradiation periods for 2 h overall.

(25) Although not described here, double-bond functionalization is possible, for example, by oxidative hydroboration, cross-methathesis, or hydroformylation.

SCHEME 9. Ab Initio Study of the Reaction Pathway



hydrolysis, demonstrating the possibility to access to this kind of new triazole with complete control of the regiochemistry.

Results obtained on compounds **2** and **13**−**18** revealed a very different behavior in azide−alkyne cycloaddition on changing the template from ester to amide. With the aim to shed light on this peculiar aspect of the reaction, an ab initio study of the reaction pathway was undertaken, and azides **15** and **43** were chosen as models of the experimental systems. These substrates were chosen for computational study since they retained the essential electronic features without the computational complexity of additional substituents on the chiral carbon atom.[26]

The transition states (TS) of the pathways for the ester and amide reaction (Scheme 9) were first localized and validated by analysis of their imaginary vibrational frequencies and of their relaxation toward reactants and products (IRC calculations)[27] with the aim to interpretate the experimental outcomes using the differences between the calculated gas-phase activation barriers.

The geometries and the energies of transition states and ground states were calculated using GAMESS(US)[28] at the B3LYP/6-31G** level of theory. The resulting reaction profiles with relative energy values and optimized geometries are displayed in Figure 1, together with the TS imaginary frequency values. Both model reactions displayed exothermic energy profile with similar activation energy values. The calculated barriers (17−19 kcal/mol) represented a plausible range for cyclization reactions requiring heating to take place.

As a matter of fact, IRC calculations did not highlight any different microscopic event, during the bond formation, that could explain the diversity observed in reactivity of amides in respect to esters. As the reaction studied is an intramolecular cycloaddition, it is plausible to imagine that the correct orbital orientation required in the TS could be reached after a conformational arrangement and that this additional event could account for the rate-determining step.

Consequently, the potential energy profile generated by scanning the C(O)═N dihedral angle of **15** was studied at the same level of theory of the transition states but with gradient convergence set to 10^{-3} hartree/bohr. The corresponding relaxed dihedral scan was performed as well for the C−O bond of **43**,

(26) Compound **43** was prepared but its cyclization to **44** did not occur under the reaction conditions explored for compound **2**.

(27) For DFT prediction of Cu-catalyzed synthesis of triazole, see: Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. J. *Am. Chem. Soc.* **2005**, *127*, 210.

(28) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *1*, 4–1347.

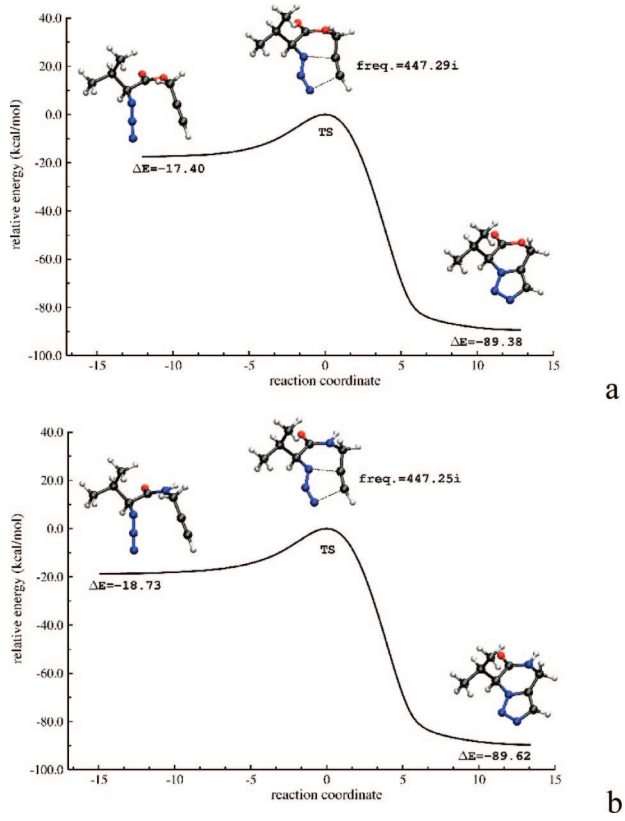


FIGURE 1. IRC energy profiles of the reactions reported in Scheme 9: TS, transition state; ΔE, energy value relative to the corresponding TS; freq, imaginary frequency value (cm^{-1}) of the TS. (a) Amide **15** as starting material. (b) Amide **43** as starting material.

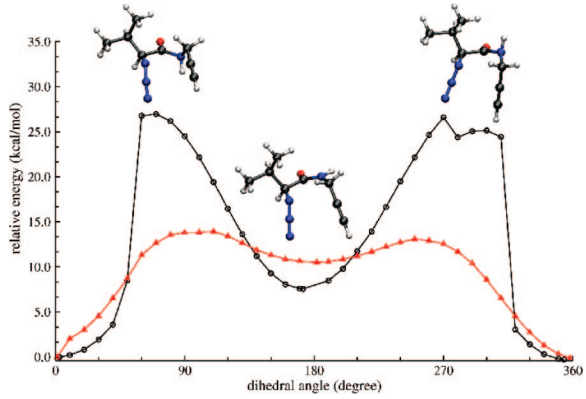


FIGURE 2. Calculated relaxed potential energy profile for the dihedral angle H−N−C═O of **15** (black). The geometries at each stationary point are shown over the curve. The corresponding potential energy profile for the equivalent conformations of **43** is also shown (red) for comparison pourposes, superimposed to the amide profile.

even if, in that case, the partially double character of the rotated bond was missing and consequently the ester group of **43** was expected to be free to rotate.

The results obtained by the dihedral scans are shown in Figure 2. They point out a different energy profile for the amide bond rotation with respect the ester. The scan around the amide bond showed two conformational transition states at approximately $\omega = \pm 90°$ ($\Delta E = 27-28$ kcal/mol), while the *cis* ($\omega = 0°$) conformer was found to be thermodynamically less stable than the *trans* ($\omega = 180°$) geometry by about 7 kcal/mol. These data were in agreement with the results reported in previous studies on amide molecular models.[29] The scan performed on the ester C−O bond showed a significantly lower activation barrier (13−14 kcal/mol). The pseudo-*cis* conformation of the ester, however, was thermodynamically less stable than the *cis* amide geometry, due to absence of partial double bond character of the rotated bond.

According to the above-reported results, this study suggest that the reactions might proceed through a two-stage mechanism involving two sequential transition states. The first (TS1) provides a conformational rearrangement required to orientate the molecule and to permit the second one (TS2) corresponding to the true cycladditions step. The main difference was found in the TS1 with the *cis* conformation of the amide found more stable than the corresponding geometry of the ester.[30] The (microwave dielectric) heating accelerates the *trans*−*cis* equilibration in the amide allowing a rapid replacement of the *cis* isomer consumed by cyclization and decreasing the amount of the oligomers formed by the other conformers. This phenomenon does not occur in the ester where all the conformers have a comparable energy and the intramolecular process may prevail.

In conclusion, we have found that intramolecular cycloaddition of azido alkynes may occur under microwave dielectric heating if the (temporary) template linkage is an amide. The intramolecular arrangements control the regiochemistry of the addition forming one of the possible isomer, that, after template cleavage, gave 1,4-disubstituted or 1,4,5-trisubstitued 1,2,3-triazoles. The differences found between amides and esters were also explained on the basis of a proposed two stage mechanism in which the bond formation is anticipated by a conformational rearrangement (preorganization step) that correctly approaches the reactive part of the molecule.

Experimental Section

(*S*)-Prop-2-ynyl, 2-Azido-3-phenylpropanoate (2). General Procedure. Propargyl alcohol (58 mg, 1.05 mmol), DMAP (0.1 mmol), and EDC (1.15 mmol) were added to a stirred solution of (*S*)-2-azido-3-phenylpropanoic acid (**1**) (200 mg, 1.05 mmol) in dry CH_2Cl_2 (6 mL) under nitrogen atmosphere. After 3 h, the solvent was evaporated and the mixture purified by flash chromatography (eluent = $CHCl_3$). Compound **2** was isolated as an oil, 168 mg (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33−7.22 (m, 5H); 4.75 (d, $J = 2$ Hz, 2H); 4.09 (m, 1H); 3.19 (dd, $J_1 = 5$, $J_2 = 14$ Hz, A of an AB system, 1H); 3.02 (dd, $J_1 = 8$, $J_2 = 14$ Hz, B of an AB system, 1H); 2.51 (t, $J = 2$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2; 135.6; 129.2; 128.7; 127.4; 75.8; 63.0; 53.1; 37.5. MS(ES+): *m/z* 252 $[M + Na]^+$. HRMS (ES+) calcd for $C_{12}H_{11}N_3NaO_2$ 252.0749, found 252.0744.

(*S*)-2-(5-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-methoxybenzyl)-3-phenylpropanamide (5). (*S*)-Prop-2-ynyl 2-azido-3-phenylpropanoate (**2**) (70 mg, 0.3 mmol) was dissolved in THF/H_2O 4:1 (1.5 mL) and submitted to microwave dielectric heating (Discover synthesizer from CEM Corp.) at 150 °C (measured by the vertically focused IR temperature sensor) for two cycles of 30 min each (max internal pressure 200 psi, max 100 W). After cooling, a white solid (21 mg) was separated and analyzed by HPLC/MS-ESI showing three peaks with *m/z* = 230 (compound

(29) Aparicio-Martinez, S.; Hall, K. R.; Balbuena, P. B. *J. Phys. Chem. A* **2006**, *110*, 9183.

(30) The activation barrier for the amide was greater than the activation barrier of the ester. However, the cycloaddition reaction exhibits the same magnitude of energy; therefore, at experimental condition of both reactions, we can exclude a discrimination through kinetic effects. It is important to point out that calculations are performed in vacuo but that the presence of the solvent should stabilize the *cis* amide conformer. See: Fisher, G. *Chem. Soc. Rev.* **2000**, *29*, 119–127.

3) and *m*/*z* = 459 and 687 (compound **4** as cyclodimer and cyclotrimer). A solution of *p*-methoxybenzylamine (0.36 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0 °C, and Me_3Al (2 M solution in toluene, 0.6 mmol) was added. After 30 min, the mixture was warmed to room temperature, and the solid obtained in the previous reaction was added. The reaction was heated at reflux for 24 h and then cooled in ice bath, and H_2O (5 mL) was added. The organic layer was separated and the aqueous phase washed with CH_2Cl_2 (5 mL × 3). The organic layers, collected together, were washed with satured NaCl(aq) (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated by rotatory evaporation under vacuum. The residue was purified by flash chromatography on silica gel (eluent = $CHCl_3$/MeOH 95:5) to give 25 mg of a yellow oil (22% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (s, 1H); 7.19−6.98 (m, 6H); 6.88 (d, J = 8 Hz, 2H); 6.68 (d, J = 8 Hz, 2H); 5.27 (t, J = 7 Hz, 1H); 4.59 (s, 2H); 4.22 (dd, J_1 = 5, J_2 = 14 Hz, A of an AB system, 1H); 4.11 (dd, J_1 = 5, J_2 = 14 Hz, B of an AB system, 1H); 3.67 (s, 3H); 3.47 (dd, J_1 = 7, J_2 = 13 Hz, A of an AB system, 1H); 3.25 (dd, J_1 = 8, J_2 = 13 Hz, B of an AB system, 1H); 2.94 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1; 159.1; 147.8; 135.3; 129.2; 128.8; 128.3; 127.4; 122.2; 114.4; 113.7; 66.0; 56.3; 55.4; 43.6; 39.4. MS(ES^+): *m*/*z* 389 [M + Na]$^+$. HRMS(ES+) calcd for $C_{20}H_{22}N_4NaO_3$ 389.1590, found 389.1584.

2-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-methoxybenzyl)-3-phenylpropanamide (7). 2-Azido-*N*-(4-methoxybenzyl)-3-phenylpropanamide (**6**) (190 mg, 0.61 mmol) was dissolved in *t*-BuOH (2 mL) and H_2O (2 mL). Propargyl alcohol (36 μL, 0.61 mmol), Cu_2SO_4 (1 mg, 0.006 mmol), and Na ascorbate (12 mg, 0.06 mmol) were added, and the mixture was stirred at room temperature for 12 h. The solvent was evaporated and the residue purified by flash chromatography on silica gel (eluent = EtOAc). Compound **7** was obtained as an yellow oil: 212 mg (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (s, 1H); 7.56 (bs, 1H); 7.12 (s, 3H); 7.01 (d, J = 2 Hz, 2H); 6.83 (d, J = 8 Hz, 2H); 6.65 (d, J = 8 Hz, 2H); 5.47 (t, J = 7 Hz, 1H); 4.53 (s, 2H); 4.20 (dd, J_1 = 6, J_2 = 14 Hz, A of an AB system, 1H); 3.99 (dd, J_1 = 4, J_2 = 14 Hz, B of an AB system, 1H); 3.76 (bs, 1H); 3.65 (s, 3H); 3.46 (dd, J_1 = 8, J_2 = 13 Hz, A of an AB system, 1H); 3.25 (dd, J_1 = 8, J_2 = 13 Hz, B of an AB system, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4; 158.9; 147.9; 135.3; 129.3; 128.9; 128.5; 122.2; 114.3; 113.9; 65.4; 55.9; 55.3; 43.6; 39.5. MS(ES^+): *m*/*z* 389 [M + Na]$^+$. HRMS(ES+) calcd for $C_{20}H_{22}N_4NaO_3$ 389.1590, found 389.1584.

(*S*)-2-Azido-3-phenyl-*N*-(prop-2-ynyl)propanamide (13). General Procedure. (*S*)-2-Azido-3-phenylpropanoic acid (**1**) (250 mg, 1.31 mmol) and propargylamine (90 μL, 1.31 mmol) were dissolved in AcOEt (10 mL), and the resulting solution was stirred at room temperature for 10 min. DMTMM (363 mg, 1.31 mmol) was added and the reaction stirred at room temperature for 12 h. The mixture was washed with HCl(aq) (1 M), saturated $NaHCO_3$(aq), and saturated NaCl(aq), dried over anhydrous Na_2SO_4, filtered, and concentrated by rotatory evaporation under vacuum. The residue was purified by flash chromatography on silica gel using CH_2Cl_2 as eluent: obtained 209 mg of an oil (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.21 (m, 5H); 6.83 (bs, 1H); 4.14 (m, 1H); 4.00−3.97 (m, 2H); 3.27 (dd, J_1 = 3, J_2 = 14 Hz, A of an AB system, 1H); 2.99 (dd, J_1 = 8, J_2 = 14 Hz, B of an AB system, 1H); 2.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7; 136.1; 129.4; 128.7; 127.3; 79.0; 71.9; 65.1; 38.4; 29.2. MS(ES^+): *m*/*z* 251 [M + Na]$^+$. HRMS(ES+): calcd for $C_{12}H_{12}N_4NaO$ 251.0909, found 251.0903.

(*S*)-2-Azido-*N*-(prop-2-ynyl)propanamide (14). Oil: 129 mg (65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.69 (bs, 1H); 4.05−3.96 (m, 3H); 2.20 (t, J = 2 Hz, 1H); 1.48 (d, J = 6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6; 78.9; 71.9; 58.9; 29.2; 16.9. MS(ES^+): *m*/*z* 175 [M + Na]$^+$. HRMS(ES^+): calcd for $C_6H_8N_4NaO$ 175.0596, found 175.0589.

(*S*)-2-Azido-3-methyl-*N*-(prop-2-ynyl)butanamide (15). Oil: 186 mg (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.05 (bs, 1H); 3.94 (m, 2H); 3.66 (d, J = 4 Hz, 1H); 2.20 (m, 1H); 2.15 (t, J = 2 Hz, 1H); 0.93 (d, J = 6 Hz, 3H); 0.81 (d, J = 6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2; 79.1; 71.5; 70.0; 31.7; 28.9; 19.4; 17.0. MS(ES^+): *m*/*z* 203 [M + Na]$^+$. HRMS(ES^+): calcd for $C_8H_{12}N_4NaO$ 203.0909, found 203.0902.

(*S*)-2-Azido-4-methyl-*N*-(prop-2-ynyl)pentanamide (16). Oil: 190 mg (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.81 (bs, 1H); 3.99 (m, 2H); 3.89 (q, J = 4 Hz, 1H); 2.20 (t, J = 2 Hz, 1H); 1.74−1.60 (m, 3H); 0.89 (d, J = 6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9; 79.0; 71.9; 62.5; 41.0; 29.2; 24.9; 23.0; 21.5. MS(ES^+): *m*/*z* 217 [M + Na]$^+$. HRMS(ES^+): calcd for $C_9H_{14}N_4NaO$ 217.1065, found 217.1060.

(*S*)-2-Azido-4-(methylthio)-*N*-(prop-2-ynyl)butanamide (17). Oil: 189 mg (68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.79 (bs, 1H); 4.12 (q, J = 4 Hz, 2H); 4.00 (m, 1H); 2.55 (m, 2H); 2.21 (t, J = 2 Hz, 1H); 2.18−2.10 (m, 1H); 2.04 (s, 3H); 2.01−1.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.0; 79.0; 72.1; 62.6; 31.4; 29.8; 29.2; 15.3. MS(ES^+): *m*/*z* 235 [M + Na]$^+$. HRMS(ES^+): calcd for $C_8H_{12}N_4OS$ 235.0630, found 235.0626.

(*S*)-*tert*-Butyl-5-azido-6-oxo-6-(prop-2-ynylamino)hexylcarbamate (18). Oil: 243 mg (60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.72 (bs, 1H); 4.61 (bs, 1H); 4.00 (m, 2H); 3.93 (m, 2H); 3.06 (d, J = 6 Hz, 1H); 2.21 (t, J = 2 Hz, 1H); 1.91−1.77 (m, 4H); 1.49−1.43 (m, 2H); 1.38 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.0; 155.9; 79.1; 78.8; 71.8; 63.8; 55.3; 31.6; 29.5; 29.0; 28.3; 22.3. MS(ES^+): *m*/*z* 332 [M + Na]$^+$. HRMS(ES^+): calcd for $C_{14}H_{23}N_5NaO_3$ 332.1699, found 332.1695.

(*S*)-2-Azido-*N*-(hex-5-en-2-ynyl)-3-phenylpropanamide (31). Yellow oil: 246 mg (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32−7.23 (m, 5H); 6.41 (bs, 1H); 5.76 (m, 1H); 5.23 (d, J = 17 Hz, 1H); 5.10 (d, J = 9 Hz, 1H); 4.17 (m, 1H, X of an ABX system); 4.08−4.06 (m, 2H); 3.33 (dd, J_1 = 3, J_2 = 14 Hz, A of an ABX system, 1H); 3.00 (dd, J_1 = 8, J_2 = 14 Hz, B of an ABX system, 1H); 2.93 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2; 136.1; 132.1; 129.5; 128.7; 127.3; 116.4; 82.9; 80.9; 65.5; 38.6; 29.7; 23.0. MS(ES^+): *m*/*z* 291 [M + Na]$^+$. HRMS(ES+): calcd for $C_{15}H_{16}N_4NaO$ 291.1222, found 291.1217.

(*S*)-2-Azido-*N*-(hex-5-en-2-ynyl)propanamide (32). Yellow oil: 176 mg (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.53 (bs, 1H); 5.67 (m, 1H); 5.20−5.12 (m, 1H); 5.02−4.95 (m, 1H); 4.00−3.87 (m, 3H); 2.85−2.82 (m, 2H); 1.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4; 132.1; 116.3; 83.6; 80.8; 59.0; 29.7; 22.9; 17.0. MS(ES^+): *m*/*z* 215 [M + Na]$^+$. HRMS(ES^+): calcd for $C_9H_{12}N_4NaO$ 215.0909, found 215.0902.

(*S*)-2-Azido-*N*-(hex-5-en-2-ynyl)-3-methylbutanamide (33). Yellow oil: 196 mg (68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.72 (bs, 1H); 5.70 (m, 1H); 5.20 (d, J = 16 Hz, 1H); 5.02 (d, J = 10 Hz, 1H); 3.98 (m, 2H); 3.71 (d, J = 4 Hz, 1H); 2.87 (m, 2H); 2.26 (m, 1H); 0.98 (d, J = 6 Hz, 3H); 0.83 (d, J = 6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9; 132.1; 116.1; 80.3; 70.2; 53.5; 31.8; 29.4; 22.9; 19.4; 17.0. MS(ES^+): *m*/*z* 243 [M + Na]$^+$. HRMS(ES^+): calcd for $C_{11}H_{16}N_4NaO$ 243.1222, found 243.1217.

(*S*)-2-Azido-*N*-(hex-5-en-2-ynyl)-4-methylpentanamide (34). Yellow oil: 215 mg (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.50 (bs, 1H); 5.69 (m, 1H); 5.19 (d, J = 16 Hz, 1H); 5.01 (d, J = 10 Hz, 1H); 3.96 (m, 2H); 3.85 (q, J = 4 Hz, 1H); 2.86 (m, 2H); 1.76−1.63 (m, 2H); 1.61−1.54 (m, 1H); 0.87 (dd, J_1 = 2, J_2 = 6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.5; 132.1; 116.3; 80.8; 62.8; 41.1; 29.7; 24.9; 23.0; 23.0; 21.5. MS(ES^+): *m*/*z* 257 [M + Na]$^+$. HRMS(ES^+): calcd for $C_{12}H_{18}N_4NaO$ 257.1378, found 257.1371.

(*R*,*S*)-7-Benzyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (19). General Procedure. (*S*)-2-Azido-3-phenyl-*N*-(prop-2-ynyl)propanamide (**13**) (50 mg, 0.22 mmol) was dissolved in CH_3CN (12 mL) and H_2O (3 mL) in a 80 mL vessel and heated under microwave conditions at 160 °C for 1 h (Discover - CEM, Method "standard": power max 250 W, ramp time 1 min, hold time 60 min, *T* 160 °C, internal pressure max 200 psi). The solvent was evaporated, giving compound **19** as a white solid that was

crystallized from EtOH/H_2O 1:1 (47 mg, 94% yield). Mp: 165−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (s, 1H); 7.20−7.10 (m, 3H); 6.80 (bs, 1H); 6.69 (d, J = 7 Hz, 2H); 5.48 (s, 1H); 4.21 (d, J = 16 Hz, 1H); 3.59 (s, 2H); 3.21 (d, J = 16 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2; 133.5; 129.6; 128.7; 128.5; 128.3; 127.8; 60.8; 39.7; 36.3. MS(ES$^+$): m/z 251 [M + Na]$^+$. HRMS(ES+): calcd for $C_{12}H_{12}N_4NaO$ 251.0909, found 251.0903. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 95/5) t_R: 77 min (85%); 85 min (15%).

(*S*)-7-Methyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (20). White solid: 31 mg (94% yield). Mp: 182−183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (s, 1H); 7.04 (bs, 1H); 5.14 (q, J = 7 Hz, 1H); 4.69 (s, 2H); 1.88 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4; 129.9; 126.2; 55.7; 36.9; 19.1. m/z [ES/MS]: 175 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_6H_8N_4NaO$ 175.0596, found 175.0590. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 95/5) t_R: 65 min (99%); 71 min (1%)

(*S*)-7-Isopropyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (21). White solid: 37 mg (93% yield). Mp: 144−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (bs, 1H); 7.60 (s, 1H); 5.04 (d, J = 3 Hz, 1H); 4.64 (s, 2H); 2.65 (m, 1H); 1.12 (d, J = 7 Hz, 3H); 0.93 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1; 129.0; 127.8; 65.5; 36.9; 34.3; 19.1; 17.4. MS(ES$^+$): m/z 203 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_8H_{12}N_4NaO$ 203.0909, found 203.0903. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 95/5) t_R: 98 min (99%); 105 min (1%)

(*S*)-7-Isobutyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (22). White solid: 40 mg (94% yield). Mp: 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (bs, 1H); 7.57 (s, 1H); 5.13 (t, J = 6 Hz, 1H); 4.63 (s, 2H); 2.11−1.98 (m, 1H); 1.97−1.87 (m, 1H); 1.76 (m, 1H); 0.91 (dd, J = 6, 11.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1; 129.1; 127.3; 58.9; 42.3; 36.6; 24.4; 22.9; 21.5. MS(ES$^+$): m/z 217 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_9H_{14}N_4NaO$ 217.1065, found 217.1059. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 95/5) t_R: 105 min (100%).

(*S*)-7-(2-(Methylthio)ethyl)-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (23). White solid 44 mg (94% yield). Mp: 71−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (bs, 1H); 7.58 (s, 1H); 5.22 (s, 1H); 4.67 (s, 2H); 2.62 (m, 1H); 2.50−2.42 (m, 3H); 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9; 129.1; 127.6; 58.4; 36.9; 31.7; 29.0; 15.0. MS(ES$^+$): m/z 235 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_8H_{12}N_4NaOS$ 235.0630, found 235.0625. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 95/5) t_R: 89 min (98%); 95 min (2%).

(*S*)-*tert*-Butyl 4-(6-Oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-7-yl)butylcarbamate (24). Yellow oil: 48 mg (70% yield), obtained after column chromatography (eluent AcOEt/MeOH 97:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (bs, 1H); 7.57 (s, 1H); 5.11 (s, 1H); 4.64 (s, 3H); 2.99 (d, J = 5 Hz, 2H); 2.30 (m, 1H); 2.19 (m, 1H); 1.40−1.35 (m, 11H); 1.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1; 156.0; 129.1; 127.5; 59.8; 40.1; 36.7; 32.9; 29.5; 28.4; 21.4. MS(ES$^+$): m/z 332 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_{14}H_{23}N_5NaO_3$ 332.1699, found 332.1694. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 95/5) t_R: 112 min (99%); 124 min (1%)

(*R*,*S*)-3-Allyl-7-benzyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (35). General Procedure. (*S*)-2-Azido-*N*-(hex-5-en-2-ynyl)-3-phenylpropanamide (**31**) (60 mg, 0.22 mmol) was dissolved in CH_3CN (12 mL) and H_2O (3 mL) in a 80 mL vessel and submitted to microwave dielectric heating at 160 °C (method "standard" as previously described) for three cycles of 1 h each. The solvent was evaporated, and the crude mixture purified by flash chromatography (eluent AcOEt): 38 mg of **35** as a light orange solid was obtained (65% yield). Mp: 121−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22−7.08 (m, 3H); 7.00 (bs, 1H); 6.71 (d, J = 7 Hz, 2H);.5.75 (m, 1H); 5.43 (m, 1H, X of an ABX system); 5.01 (dd, J_1 = 1, J_2 = 10 Hz, 1H); 4.93 (dd, J_1 = 1, J_2 = 17 Hz, 1H); 4.07 (dd, J_1 = 3, J_2 = 15 Hz, 1H); 3.57 (d, J = 3 Hz, 2H); 3.42 (dd, J_1 = 6, J_2 = 16 Hz, 1H, A of an ABX system); 3.31 (dd, J_1 = 6, J_2 = 16 Hz, 1H, B of an ABX system); 3.08 (d, J = 16 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4; 139.3; 133.7; 133.6; 129.6; 128.4; 127.8; 125.6; 116.8; 60.7; 39.7; 36.3; 29.7. MS(ES$^+$): m/z 291 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_{15}H_{16}N_4NaO$ 291.1222, found 291.1217. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 90/10) t_R: 65 min (85%); 69 min (15%).

(*S*)-3-Allyl-7-methyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (36). Yellow solid: 27 mg (64% yield). Mp: 122−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (bs, 1H); 5.90 (m, 1H); 5.12−5.05 (m, 3H); 4.54 (s, 2H); 3.48 (d, J = 6 Hz, 2H); 1.85 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8; 139.9; 133.8; 123.7; 117.2; 55.7; 36.9; 30.0; 19.2. MS(ES$^+$): m/z 215 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_9H_{12}N_4NaO$ 215.0909, found 215.0902. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 90/10) t_R: 89 min (98%); 93 min (2%).

(*S*)-3-Allyl-7-isopropyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (37). Yellow solid: 31 mg (64% yield). Mp: 112−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (bs, 1H); 5.91 (m, 1H); 5.12−5.00 (m, 3H); 4.50 (s, 2H); 3.50 (m, 2H); 2.64 (m, 1H); 1.11 (d, J = 6 Hz, 3H); 0.94 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9; 139.5; 133.9; 124.9; 117.0; 65.5; 37.0; 34.4; 29.9; 19.0; 17.5. MS(ES$^+$): m/z 243 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_{11}H_{16}N_4NaO$ 243.1222, found 243.1216. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 90/10) t_R: 100 min (99%); 104 min (1%).

(*S*)-3-Allyl-7-isobutyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (38). Yellow oil: 36 mg (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (bs, 1H); 5.91 (m, 1H); 5.12−5.08 (m, 3H); 4.52 (m, 2H); 3.49 (d, J = 6 Hz, 2H); 2.04−1.99 (m, 1H); 1.96−1.89 (m, 1H); 1.79 (m, 1H); 0.93 (t, J = 6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9; 139.8; 133.9; 124.1; 117.1; 59.0; 42.4; 36.7; 30.0; 24.4; 22.8; 21.8. MS(ES$^+$): m/z 257 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_{12}H_{18}N_4NaO$ 257.1378, found 257.1371. HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 95/5) t_R: 39 min (100%). HPLC (Chiral Column Chiralpack 1B 0.46 cm × 15 cm; hexane/*i*-PrOH: 90/10) t_R: 98 min (99%); 102 min (1%).

Ethyl 2-(7-Benzyl-6-oxo-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)acetate (25). General Procedure. 7-Benzyl-4,5-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (**19**) (50 mg, 0.22 mmol) and ethyl bromoacetate (27 μL, 0.24 mmol) were added to a suspension of NaH (17.6 mg, 0.44 mmol) (previously washed with petroleum ether) in dry DMF (1 mL) at room temperature. The mixture was submitted to microwave dielectric heating at 100 °C for 30 min. The solution was diluted with AcOEt (15 mL) and washed with H_2O (5 mL × 5). The organic phase was dried over dry Na_2SO_4 and filtered and the solvent evaporated, obtaining compound **25** as a yellow oil (46 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (s, 1H); 7.20−7.08 (m, 3H); 6.68 (d, J = 7 Hz, 2H); 5.57 (t, J = 3 Hz, 1H); 4.37 (d, J = 7 Hz, 1H); 4.27 (d, J = 15 Hz, 1H); 4.17 (q, J = 7 Hz, 2H); 3.74 (d, J = 17 Hz, 1H); 3.60 (m, 2H); 3.37 (d, J = 15 Hz, 1H); 1.24 (t, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6; 165.1; 133.5; 129.5; 128.6; 128.5; 128.0, 127.7; 61.7; 60.7; 48.0; 42.5; 40.0; 14.1. MS(ES$^+$): m/z 337 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_{16}H_{18}N_4NaO_3$ 337.1277, found 337.1270.

5,7-Dibenzyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (26). Oil: 42 mg (60% yield), after column chromatography (eluent AcOEt/petroleum ether (40−60 °C) 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29−7.19 (m, 5H); 7.08−7.04 (m, 2H); 6.90 (t, J = 7 Hz, 2H); 6.53 (d, J = 7 Hz, 2H); 5.54 (m, 1H, X of an ABX system); 4.56 (d, J = 14 Hz, 1H); 4.41 (d, J = 14 Hz, 1H); 3.98 (d, J = 15 Hz, 1H); 3.57 (m, 2H, AB of an ABX system); 2.97 (d, J = 16 Hz, 1H). MS(ES$^+$): m/z 341 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_{19}H_{18}N_4NaO$ 341.1378, found 341.1371.

3-Allyl-5,7-dibenzyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (39). Compound **39** was obtained after only 15 min of

microwave heating. Yellow oil: 51 mg (65% yield), obtained after column chromatography (eluent AcOEt/petroleum ether (40−60 °C) 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29−7.26 (m, 3H); 7.12−7.08 (m, 3H); 6.93 (t, J = 7 Hz, 2H); 6.57 (d, J = 7 Hz, 2H); 5.69 (m, 1H); 5.52 (m, 1H, X of an ABX system); 4.94 (dd, J_1 = 1, J_2 = 10 Hz, 1H); 4.84 (dd, J_1 = 1, J_2 = 17 Hz, 1H); 4.59 (d, J = 6 Hz, 1H); 4.43 (d, J = 14 Hz, 1H); 3.88 (d, J = 16 Hz, 1H); 3.62 (dd, J_1 = 2, J_2 = 13 Hz, 1H, A of an AB system); 3.55 (dd, J_1 = 4, J_2 = 13 Hz, 1H, B of an AB system); 3.34 (dd, J_1 = 6, J_2 = 16 Hz, 1H); 3.23 (dd, J_1 = 6, J_2 = 16 Hz, 1H); 2.88 (d, J = 16 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5; 139.1; 134.7; 133.7; 129.9; 129.6; 129.5; 129.0; 128.7; 128.4, 128.3; 128.3; 128.2; 128.0; 125.7; 116.6; 60.7; 50.5; 40.1; 40.0; 29.5. MS(ES$^+$): m/z 381 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_{22}H_{22}N_4NaO$ 381.1691, found 381.1687.

2-(5-(Aminomethyl)-1*H*-1,2,3-triazol-1-yl)-3-phenylpropanoic Acid (27). General Procedure. A 6 M solution of HCl(aq) (2.7 mL) was added to 7-benzyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (**19**) (50 mg, 0.22 mmol), and the mixture was heated under microwave conditions at 85 °C for three periods of 1 h each. The solution was extracted with $CHCl_3$ (4 × 3 mL) and the water layer evaporated under vacuum to give compound **27** as a light orange waxy material (46 mg, 85% yield). ^{1}H NMR (400 MHz, MeOD) δ: 7.95 (bs, 1H); 7.17−7.06 (m, 6H); 5.82 (1H, X of an ABX system); 4.12 (d, J = 16 Hz, 1H); 3.93 (d, J = 15 Hz, 1H); 3.63 (2H, AB of an ABX system). ^{13}C NMR (100 MHz, MeOD) δ: 168.8; 135.8; 133.1; 132.4; 128.8; 128.4; 127.0; 63.3; 36.6, 31.6. MS(ES$^+$): m/z 269 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_{12}H_{14}N_4NaO_2$ 269.1014, found 269.1008.

2-(4-Allyl-5-(aminomethyl)-1*H*-1,2,3-triazol-1-yl)-3-phenylpropanoic Acid (40). Orange waxy material: 53 mg (84% yield). ^{1}H NMR (400 MHz, MeOD) δ: 7.15−7.04 (m, 6H); 5.90−5.78 (m, 2H); 5.04 (d, J = 10 Hz, 1H); 4.89 (m, 1H); 3.97 (d, J = 15 Hz, 1H); 3.86 (d, J = 15 Hz, 1H); 3.71 (m, 1H); 3.57−3.45 (m, 3H). ^{13}C NMR (100 MHz, MeOD) δ: 169.2; 145.0; 135.8; 129.4; 129.0; 128.7; 128.2; 127.9; 127.6; 126.4; 116.5; 63.6; 35.9; 29.3; 28.1. MS(ES$^+$): m/z 309 [M + Na]$^+$. HRMS(ES$^+$): calcd for $C_{15}H_{18}N_4NaO_2$ 309.1327, found 309.1321.

2-(4-Allyl-5-((benzylamino)methyl)-1*H*-1,2,3-triazol-1-yl)-3-phenylpropanoic Acid (41). HCl concd (1 mL) was added to 3-allyl-5,7-dibenzyl-4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one (**39**) (40 mg, 0.11 mmol), and the mixture was submitted to microwave dielectric heating at 150 °C for three periods of 1 h each. The solution was evaporated and the crude reaction purified by flash chromatography (eluent AcOEt), obtaining compound **41** as a yellow waxy material (17 mg, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31−7.29 (m, 2H); 7.18−7.09 (m, 4H); 6.96−6.91 (m, 2H); 6.59 (d, J = 7 Hz, 2H); 5.55−5.48 (m, 2H); 4.63−4.46 (m, 2H); 4.02−3.93 (m, 2H); 3.67−3.55 (m, 4H); 3.00 (d, J = 16 Hz, 2H). MS(ES$^+$): m/z 399 [M + Na]$^+$. HRMS(ES$^+$) calcd for $C_{22}H_{24}N_4NaO_2$ 399.1797, found 399.1791.

***N*-2-(Hex-5-en-2-ynyl)phthalimide (29).** A mixture of propargyl phthalimide (**28**) (2.9 g, 15.67 mmol), allyl bromide (2.04 mL, 23.51 mmol), Na_2SO_3 (988 mg, 7.84 mmol), K_2CO_3 (2.16 g, 15.67 mmol), DBU (1.25 mL, 8.37 mmol), and CuI (597 mg, 3.13 mmol) was stirred at room temperature in DMF (25 mL) for 2 h. The solution was then diluted with Et_2O (70 mL) and washed with H_2O (25 mL × 5). The organic phase was dried over dry Na_2SO_4, filtered, and evaporated, obtaining compound **29** as a white solid (3.33 g, 95% yield). Mp: 82−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (m, 2H); 7.66 (m, 2H); 5.68 (m, 1H); 5.21 (d, J = 18 Hz, 1H); 5.00 (d, J = 10 Hz, 1H); 4.39 (s, 2H); 2.85 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1; 134.1; 132.0; 132.0; 123.4; 116.3; 80.1; 75.9; 27.4; 22.9. MS(ES$^+$): m/z 248 [M + Na]$^+$. HRMS(ES+): calcd for $C_{14}H_{11}NNaO_2$ 248.0687, found 248.0681.

Hex-5-en-2-yn-1-amine (30). *N*-2-(Hex-5-en-2-ynyl)phthalimide (**29**) (600 mg, 2.66 mmol) was dissolved in a 33% solution of $MeNH_2$ in absolute EtOH (5 mL). The mixture was heated under microwave conditions at 70 °C for 10 min. The crude reaction was filtered twice over Celite with Et_2O, and the solvent was evaporated to obtain compound **30** as a yellow oil (243 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.79 (m, 1H); 5.27 (d, J = 11 Hz, 1H); 5.08 (d, J = 9 Hz, 1H); 3.42 (s, 2H); 2.93 (s, 2H); 1.49 (bs, 2H). The product was not further purified and was used at this level of purity in the synthesis of compounds **31**−**34**.

Computational Details. All of the structures were constructed by Ghemical[31] software package and were optimized with MPQC[32] software at the HF level of theory using the 6-21G basis set. All fine calculations were performed at the DFT level using the B3LYP[33] hybrid functional and 6-31G** basis set on vacuum within GAMESS(US) software, and the results were visualized with MOLDEN[34] or VMD[35] software packages. Within the $CONTRL group of options, QMTOLL was set to 10^{-6} and ICUT was set to 11. The DIRSCF flag ($SCF group) was activated. Stationary points characterized as transition state showed the proper number of imaginary harmonic vibrational frequencies. Molecular geometries were fully optimized with gradient convergence set to 10^{-4} hartree/bohr. In the saddle point searches, the Hessian was updated with the mixed Murtagh−Sargent/Powell procedure.[36] Intrinsic reaction coordinate (IRC) calculations were used to verify the adjacent local minima. IRC were traced at the B3LYP/6-31G** level of theory from transition states toward both reactants and product directions using the Gonzàlez−Schlegel algorithm.[37] Potential energy profile calculations for the dihedral angles (see the Results and Discussion) were performed with same level of theory but with gradient convergence set to 10^{-3} hartree/bohr.

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Supporting Information Available: Chromatographic and spectroscopic characterization of compounds **2**, **3**, **5**−**7**, **13**−**27**, and **29**−**41** and atom coordinates and energies for compounds **15** and **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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