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Thermal Intramolecular [4 + 2] Cycloadditions of Allenamides: A Stereoselective Tandem Propargyl Amide Isomerization–Cycloaddition

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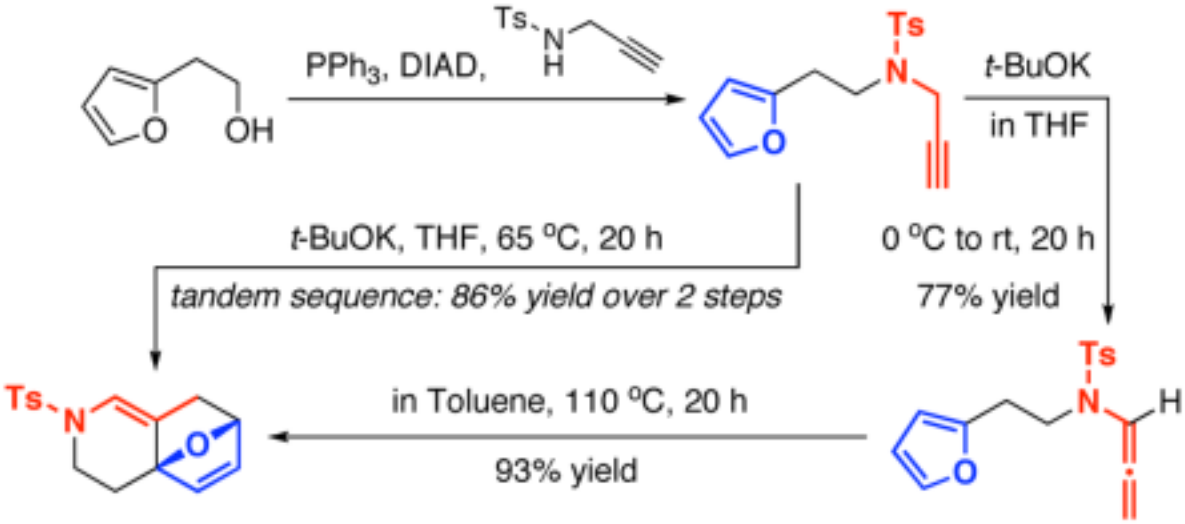
Abstract



A stereoselective intramolecular normal demand [4 + 2] cycloaddition of allenamides under thermal conditions without metal assistance is described. This work led to the development of a stereoselective tandem propargyl amide-isomerization–[4 + 2] cycloaddition sequence amenable for rapid assembly of complex nitrogen heterocycles.

We have been embarking on the chemistry of allenamides in the last ten years.[1,2] In particular, allenamides have proven to be an excellent source of nitrogen-stabilized oxyallyl cations[3,4] through DMDO-epoxidation, thereby allowing us to develop highly stereoselective [4 + 3] cycloaddition manifolds[5–7] including intramolecular[8,9] cycloadditions such as using *N*-tethered allenamide **1**[9] en route to synthetically useful nitrogen heterocycle **3** [Scheme 1]. However, the dependence on DMDO as the key oxidant for the transformation can pose a challenge in terms of scale and operational convenience. Mascareñas's report[10] intrigued us because of their usage of $PtCl_2$/CO in catalyzing a [4 + 3] cycloaddition of allenes. More significantly, they also documented that a different catalyst [AuCl] could effectively direct the

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Supporting Information Available: Experimental and ^{1}H NMR spectral and characterizations for all new compounds as well as X-ray structrural data available free of charge at http://pubs.acs.org.

reactivity toward the competing [4 + 2] cycloaddition instead of the [4 + 3] cycloaddition. Recently, Toste[11] revealed a similar divergence in [4 + 2] versus [4 + 3] cycloaddition when using different ligands along with a Au(I) catalyst. Our own efforts in exploring Mascareñas's $PtCl_2$ versus AuCl protocol[10,12,13] while adopting allenamides led us to an interesting and different direction than the initially anticipated issues regarding competing [4 + 3] and [4 + 2] cycloadditions [see **4**-TS^{4+3}→**6** vs. **4**-TS^{4+2}→**7**, respectively, in Scheme 1]. We report here a rare normal electron-demand[1,14–17] [4 + 2] cycloaddition involving electron-rich heteroatom-substituted allenes under thermal conditions and a stereoselective tandem propargyl amide isomerization–intramolecular [4 + 2] cycloaddition sequence.

To commence our studies, we initially examined an *N*-Boc- substituted allenamide, but it was not useful for platinum and gold protocols [see footnote 18 for results]. Consequently, *N*-sulfonyl-allenamide **9**[19] was prepared from propargyl amide **8** via our base-promoted isomerization protocol using cat *t*-BuOK.[20] We quickly found that with the exception of AuCl [entries 5–7 in Table 1], platinum catalysts [entries 1–4] and Au(III) catalyst [entry 9] were not useful in generating any cycloaddition types of products. Concentrations did not appear to have any impact, as reactions run at 0.04 *M* led to the same outcome.

Most intriguingly, the illustration of the corresponding [4 + 2] cycloadduct **10** shown in Table 1 of hindsight after a series of subsequent studies. As shown in Figure 1, although **10** and its regioisomer **11** are readily distinguishable, it is not obvious how to unambiguously distinguish **10** from potential [4 + 3] cycloadduct **12** solely based on the key ^{1}H NMR resonances. However, as we continued our explorations and began to achieve high yielding reactions with silver salts [entries 10–13], Brønsted acids [entries 14 and 15, and then, ultimately simple thermal conditions with [entry 16] or without 4Å MS [entry 17], we recognized that this did not appear to be a simple [4 + 3] cycloaddition process. Instead, it turned out to be exclusively a [4 + 2] cycloaddition pathway under all conditions after attaining an X-ray crystal structure [*vide infra*].

The ability to pursue this cycloaddition thermally represents a unique opportunity for two major reasons. Firstly, as shown in Table 2, this thermally driven allenic-[4 + 2] cycloaddition manifold possesses a much broader synthetic potential than previous work.[10,11]

The substrate scope is comprised of: (1) Different *N*-substituents [entries 1–3] including carbamates; (2) substitutions at the allenic γ-position [(±)-**15a** and (±)-**15b** in entries 4 and 5, respectively] that gave the respective cycloadducts **16a** and **16b** with the major isomers shown as assigned via nOe experiments [Figure 2]; (3) various furan substitutions [entries 6 and 7]; (4) a longer tethering that led to the regiochemical outcome in favor of the internal olefin of the allenic motif [**22** in entry 8], which is found as a single diastereomer;[21] and also notably in this case, when using 10 mol% of $AgBF^4$ and 4Å MS, **22** was isolated in 58% yield as the only regioisomer after heating in toluene at 110 °C for 36 h;[21] and lastly, (5) a simple butadiene [entry 9].

The X-ray structure of cycloadduct **14a** unambiguously confirms the [4 + 2] cycloaddition pathway [Figure 2], and it provides a general mechanistic picture for this allenic cycloaddition. Based on the nOe assignments of the respective major isomers for **16a** and **16b** [*dr* 3:1], the current mechanistic picture also implies that the furan approaches from the more hindered side with R ≠ H. We are not certain of reasons behind this contra-steric approach.

Secondly and more importantly, we recognized the possibility of developing a tandem sequence consisting of propargyl amide isomerization followed by cycloaddition. As shown in Scheme 2, In the presence of 20 mol% *t*-BuOK at 65 °C, isomerization of propargyl amide **8** and the ensuing cycloaddition led to **10** in 86% yield over three steps furan [or two steps from commercially available 2-(furan-2-yl)ethanol **26**]. Likewise, cycloadduct **29** could be

obtained in 68% yield in two steps from furfuryl alcohol. We note here that without *t*-BuOK, this tandem process does not take place even after heating in toluene at 110 °C for 24 h, thereby suggesting that the tandem sequence proceeds through exclusively the respective allenamide intermediate.

In addition, with platinum or gold catalysts, the reaction proceeded through a very different pathway.[22,23] Moreover, in a related example from Kanemastu's account,[15] 5.0 equiv of *t*-BuOK was used and the reaction afforded ring-opened and aromatized products instead of furan-cycloadduct **29**. The use of catalytic amount of *t*-BuOK proves to be the key in accessing these structurally more useful cycloadducts.

Finally, this tandem process is general for a range of propargyl amides [Table 3] including those that are terminally substituted [entries 2–4], thereby also representing first examples of successful based-promoted isomerizations of terminally substituted propargyl amides to allenamides.[20,24] It is noteworthy that all propargyl amides employed here were prepared from respective furyl alcohols featuring a Mitsunobu reaction using *N*-sulfonylated propargyl amine [see **27** in Scheme 2], allowing this tandem process amenable for facile constructions of complex nitrogen heterocycles from very simple commercially available material.

We have described here a rare normal electron-demand [4 + 2] cycloaddition of *N*-tethered allenamides under thermal conditions without assistance of any metals. Our efforts also led to the development of an efficient and highly stereoselective tandem propargyl amide-isomerization–[4 + 2] cycloaddition sequence amenable for rapid assembly of highly functionalized nitrogen heterocycles from very simple commercial furyl alcohols. Applications of this method toward constructing isoquinoline, quinoline, or isoindole containing natural products are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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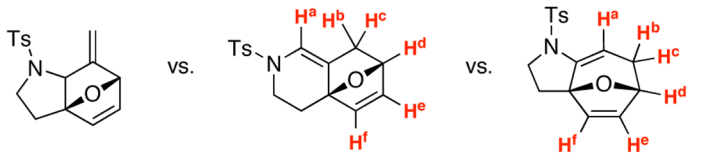
18. When utilizing a Boc-substituted allenamide [see i], reactions promoted by $PtCl_2$, $PtCl_4$, AuCl, or $AuCl_3$ [in 10–100 mol % at rt-65 °C] led to very low yields of possible cycloadduct [ii] with mostly being hydrolysis of the starting allenamide and decomposition. Only when using $AgSbF_6$, a modest yield was attained for cycloadduct ii.
19. See Supporting Information.
20. (a) Wei LL, Mulder JA, Xiong H, Zificsak CA, Douglas CJ, Hsung RP. Tetrahedron 2001;57:459. (b) Xiong H, Hsung RP, Wei LL, Berry CR, Mulder JA, Stockwell B. Org Lett 2000;2:2869. [PubMed: 10964386]
21. nOe experiments of cycloadduct 22 and its possible cycloaddition transition state.In addition, the regioisomeric cycloadduct 23 was found to equilibrate to 22 via retro-[4 + 2] and [4 + 2] after heating at 110 °C in toluene for 22 h.
22. When using $PtCl_4$, we were able to isolate some products [iii and iv] that are related to those reported by Hashmi amd Echavarren [see reference 23].
23. For a leading reference, see: (a)Hashmi ASK, Salathé R, Frey W. Chem Eur J 2006;12:6991.(b) Hashmi ASK, Frost TM, Bats JW. J Am Chem Soc 2000;122:11553.(c)Martín-Matute B, Cárdenas DJ, Echavarren AM. Angew Chem Int Ed 2001;40:4754.
24. For a review, see: Tracey MR, Hsung RP, Antoline J, Kurtz KCM, Shen L, Slafer BW, Zhang Y. Weinreb, Steve M.Science of Synthesis, Houben-Weyl Methods of Molecular Transformations Georg Thieme Verlag KGChapter 21.42005;



11: *[4 + 2]* **10:** *[4 + 2]* **12:** *[4 + 3]*

δ ppm: 6.60 (s, H^a); 2.53 (dd, H^b, *J* = 4.5, 14.0 Hz); 1.91 (d, H^c, *J* = 14.0 Hz)
5.02 (dd, H^d, *J* = 1.5, 4.5 Hz); 6.32 (d, H^e, *J* = 5.5 Hz); 6.04 (d, H^f, *J* = 5.5 Hz)

Figure 1.
[4 + 2] Versus [4 + 3] Cycloadducts.
δppm: 6.60 (s, $\mathbf{H^a}$); 2.53 (dd, $\mathbf{H^b}$, *J* = 4.5, 14.0 Hz); 1.91 (d, $\mathbf{H^c}$, *J* = 14.0 Hz) 5.02 (dd, $\mathbf{H^d}$, *J* = 1.5, 4.5 Hz); 6.32 (d, $\mathbf{H^e}$, *J* = 5.5 Hz); 6.04 (d, $\mathbf{H^f}$, *J* = 5.5 Hz)

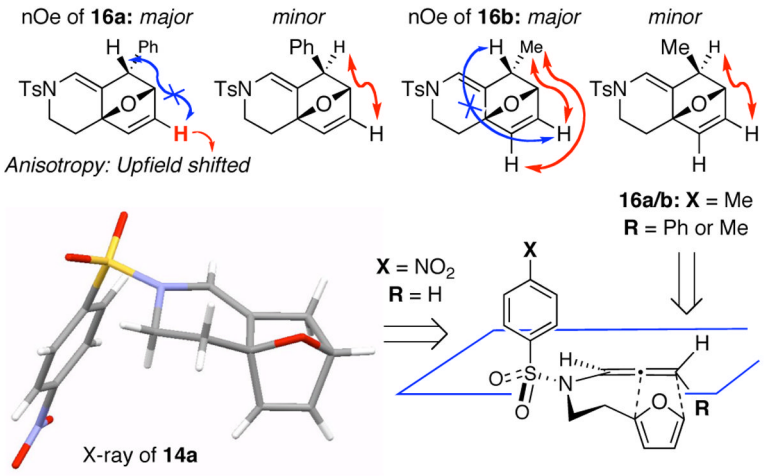
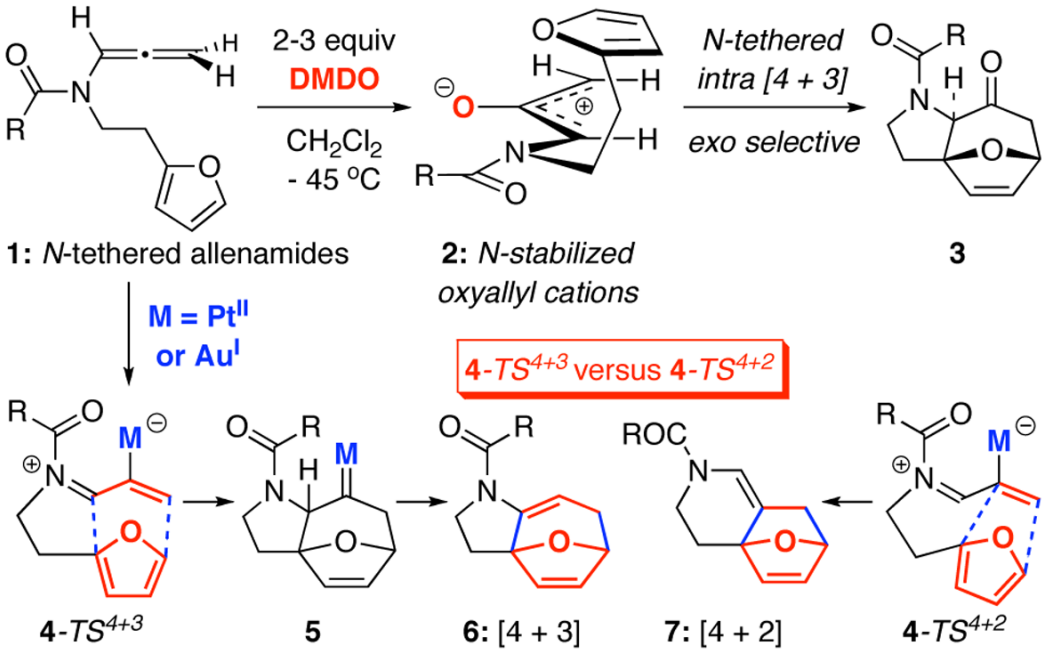
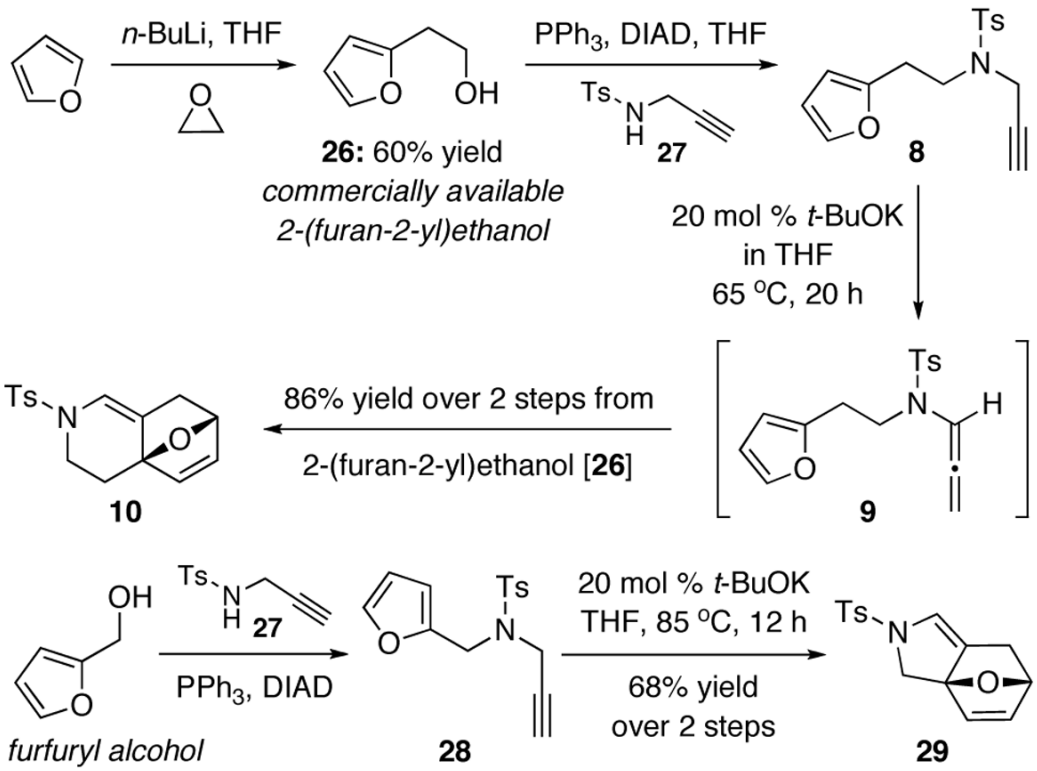


Figure 2.
nOes Experiments and X-Ray Structure of **14a**.



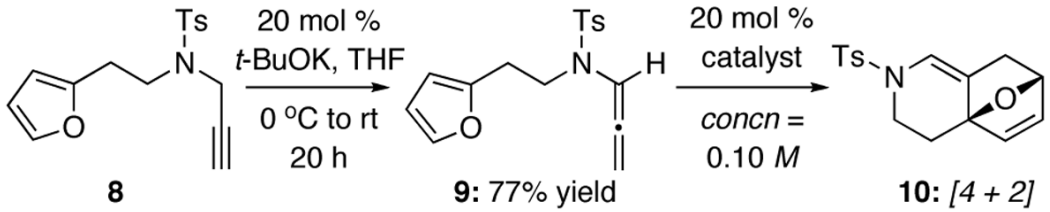
Scheme 1.
Cycloadditions of *N*-Tethered Allenamides.



Scheme 2.
A Tandem Propargyl Amide-Isomerization–[4 + 2].

Table 1

Exploring Conditions for the Cycloaddition.



8 **9:** 77% yield **10:** *[4 + 2]*

entry	catalysts	4 Å MS	solvents	temp [°C]	time [h]	yield [%][a]
1	$PtCl_2$	√	DCE	65	<12	0
2	$PtCl_4$	√	DCE	65	3	13[c]
3	$PtCl_4$	√	THF	65	6	15[c]
4	$PtCl_4$	√	toluene	23	1	11[c]
5	AuCl	√	DCE[b]	23	10min	66
6	AuCl	√	THF	65	6	35[c]
7	AuCl	√	toluene	65	<30 min	42[c]
8	$AuCl/AgSbF_6$	√	DCE	23	1	16[c]
9	$AuCl_3$	√	DCE	65	10 min	0
10	$AgSbF_6$	√	DCE	65	6	85[c]
11	$AgBF_4$	√	DCE	65	6	94
12	$AgBF_4$	√	toluene	65	6	80[c]
13	$AgBF_4$	√	THF	65	<12	57[c]
14	CSA[d]	√	DCE	65	<12	92[c]
15	PPTS[d]	√	DCE	65	8	94[c]
16	***No***	√	**THF**	**65**	**30**	**91**[c]
17	***No***	**No**	***d_8*-toluene**	**110**	**20**	**93**

[a] Isolated yields unless otherwise indicated.

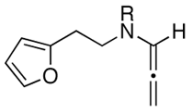
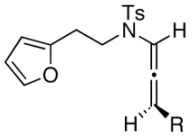
[b] DCE: 1,2-Dichloroethane.

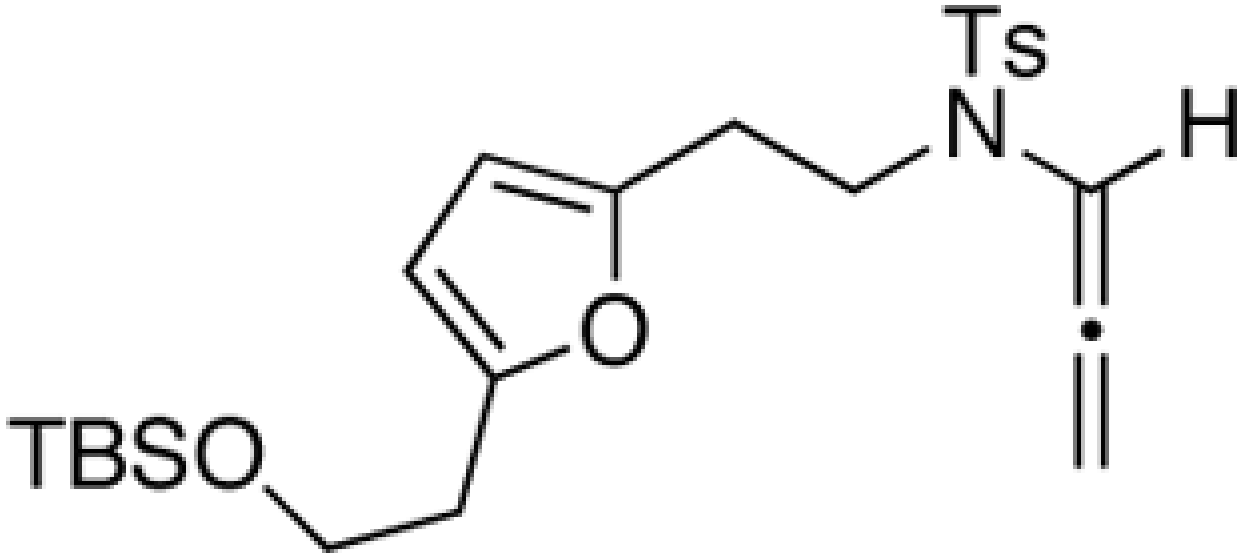
[c] NMR yields determined with phenanthrene as the internal standard

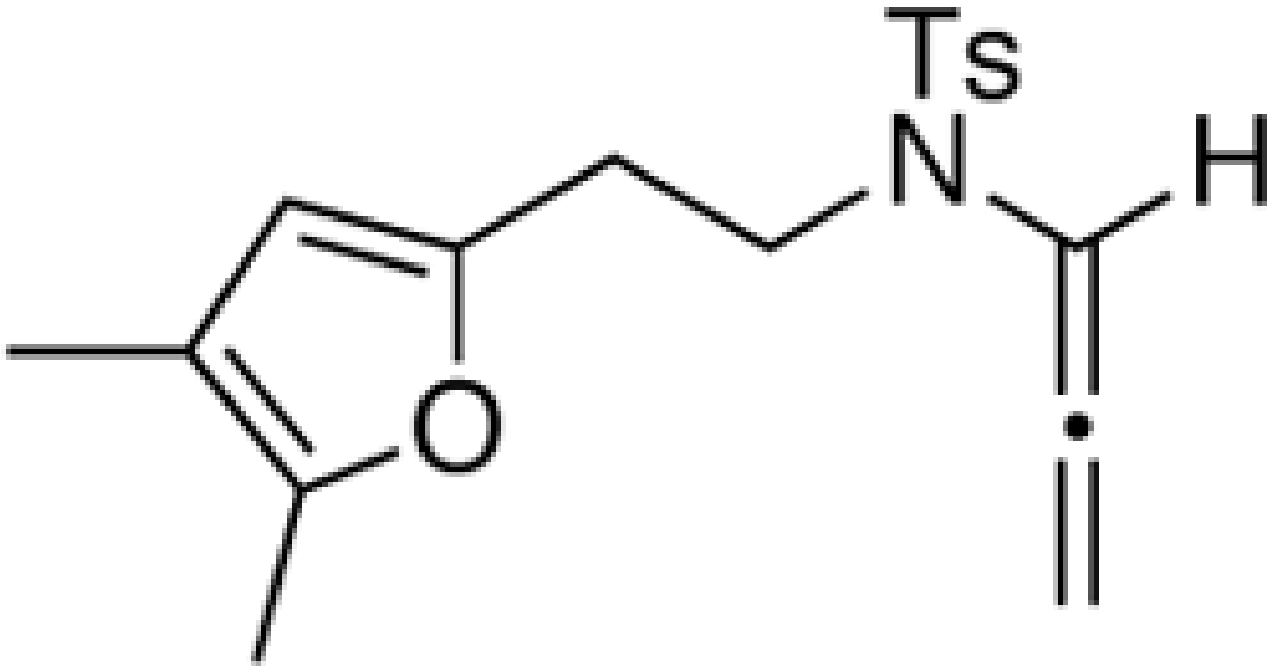
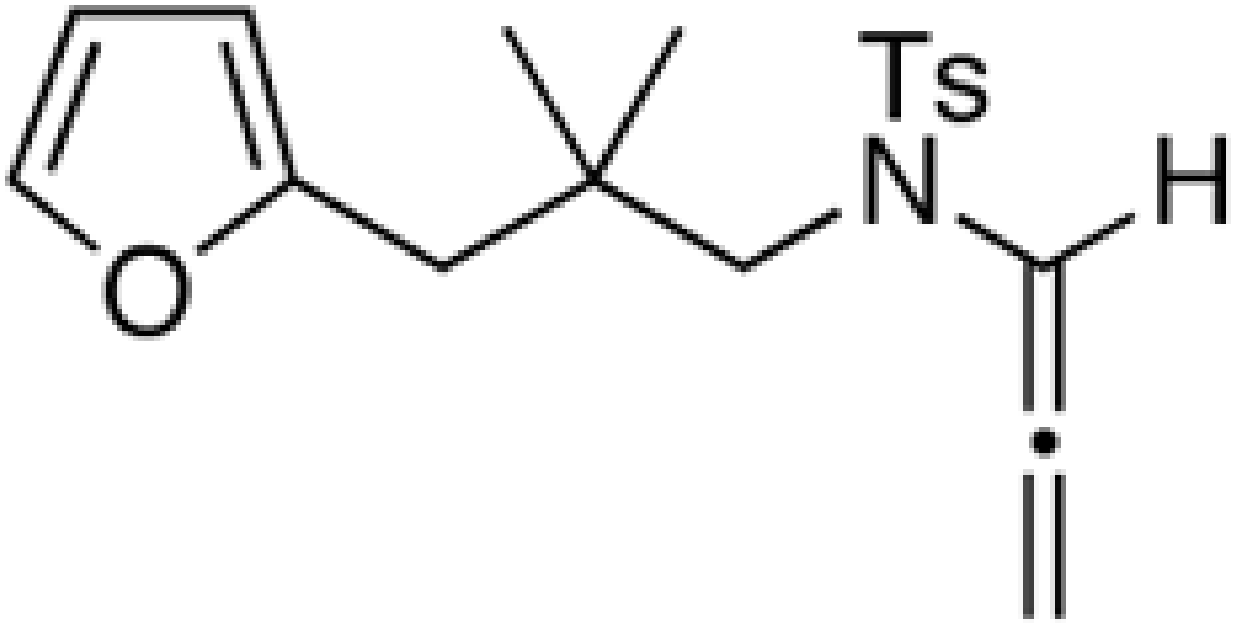
[d] 10 mol % was used.

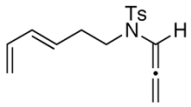
Table 2

Thermal [4 + 2] Cycloaddions of of Allenamides.

entry	allenamides[a]
	
1	**13a:** R = *p*-Ns
2	**13b:** R = Boc
3	**13c:** R = (−)-menthyl
	
4	(±)-**15a:** R = Ph
5	(±)-**15b:** R = Me
6	**17**



entry	allenamides[a]
7	**18** 
8	**21** 

entry	allenamides[a]
9	**24** 

[a] Unless otherwise noted, all reactions were carried out in THF at 85 °C at *concn* = 0.10 *M*. Reactions in entries 3 and 8 were run in toluene. Entries 4 and 8 were run at 45 °C and 110 °C, respectively.

[b] Isolated yields.

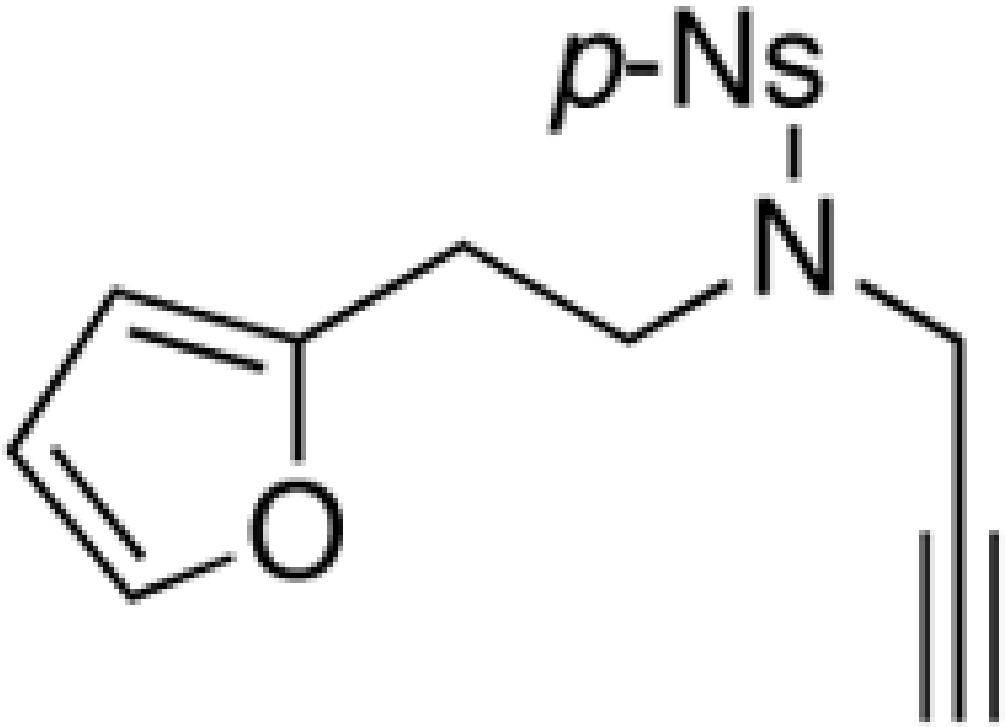
[c] Only one isomer by ^{1}H NMR but absolute configuration unassigned.

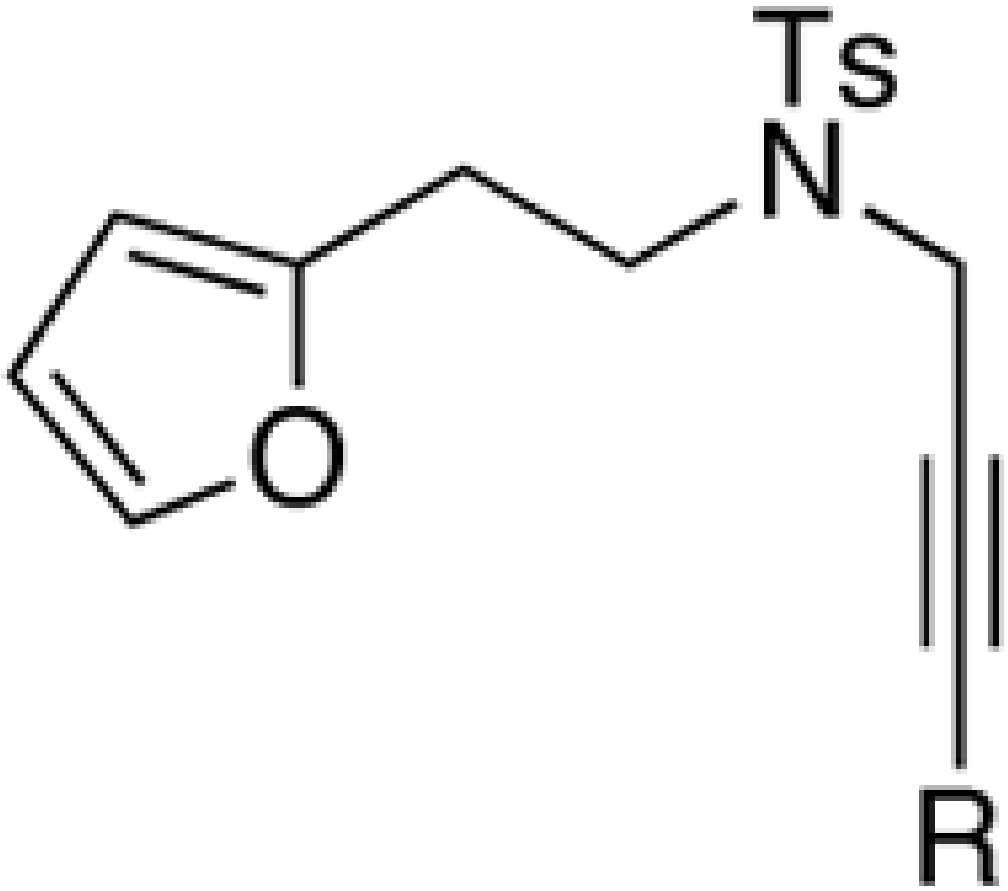
[d] **16a** and **16b** were found as a ~ 3:1 inseparable isomeric mixture.

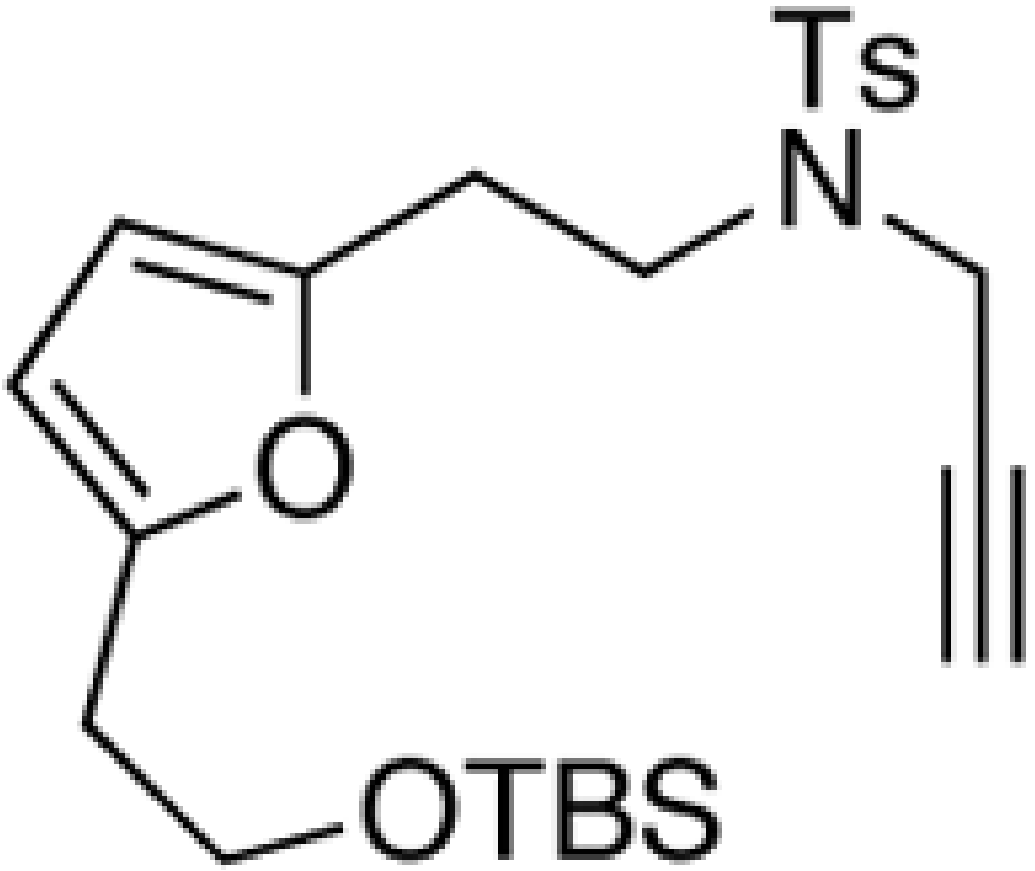
[e] Regioisomeric ratio of regioisomers **22** and **23** is ~ 4:1.

Table 3

Tandem Isomerization–[4 + 2] Cycloadditions.

entry	propargyl amides[a]	time [h]
1		24
	30	

entry	propargyl amides[a]	time [h]
2		24
3		24
4		16

entry	propargyl amides[a]	time [h]
5	 **32**	14

[a] Unless otherwise noted, all reactions were carried out in THF at *concn* = 0.10 *M* with 20 mol % of *t*-BuOK. For entries 1 and 5: Reaction temp = 65 °C; for entries 3 and 4: temp = 85 °C; and for entry 2: temp = 25 °C.

[b] Isolated yields.

[c] *dr* = ~3:1.

[d] *dr* = ~2:1.

[e] The reaction was slower, and also observed was hydrolysis of the starting allenamide.