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Regio- and Stereoselective Isomerizations of Allenamides: Synthesis of 2-Amido-Dienes and Their Tandem Isomerization–Electrocyclic Ring-Closure

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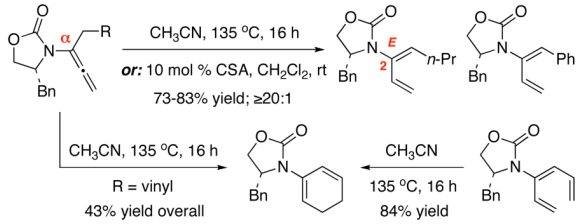
Abstract



A regio- and stereoselective isomerization of allenamides is described, leading to preparations of *de novo* 2-amido-dienes and a tandem isomerization–6π-electron electrocyclic ring-closure.

Synthesis of conjugated dienes via an allene isomerization, while a thermodynamically favored process, is not trivial kinetically. The required 1,3-H-shift constitutes a four-electron [2π + 2σ] process that would call for an antarafacial approach if proceeding through a concerted and anti-Hückel [or Möbius] transition state.[1,2] Although impossible in an allylic system, it is relatively more feasible for an allenic system because of the presence of orthogonally oriented *p*-orbitals of the *sp*-hybridized central allenic carbon [Scheme 1]. The orthogonal *p*-orbital at C3 [in blue] introduces a formal phase change required for an anti-Hückel transition state, or formally allows a six-electron [2π +2σ + 2π] process when the second set of allenic π-electrons becomes involved. Nevertheless, the calculated[2a] ΔE_{act} value remains high at 77.7 kcal mol^{-1} and consequently, concerted or not, most thermal isomerizations of allenes take place at high temperatures,[3,4] thereby rendering it difficult to control *E/Z* ratios of the resulting dienes. There are more practical approaches would involve stepwise processes promoted by acid, base, or metal, but their examples are limited and the level of stereo- and regiochemical control need to be improved.[3,5]

Given that most dienes can be prepared from an array of stereoselective transformations, synthesizing conjugated dienes from structurally more challenging allenes through a kinetically demanding and stereochemically undistinguished isomerization does not appear to be a logical first choice. However, our efforts with the chemistry of allenamides[6] allowed us to envision a much greater potential in constructing amido-dienes through isomerizing allenamides[7–9] because there are no consistent approaches for synthesizing amido-dienes.[10–12] Of the two major methods for preparing amido-dienes,[10] the one involving acid-mediated condensations suffers from functional group tolerance with the metal-mediated amidative

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cross-coupling[13,14] suffering from limited access to halo-dienes [Scheme 1]. In contrast, substituted allenamides are quite accessible through α-alkylations of parent allenamide[15,16] or amidative cross-couplings of allenyl halides.[17] Their isomerizations can prove to be an invaluable entry to amido-dienes. We communicate here a regio- and stereoselective isomerization of allenamides in the synthesis of 2-amido-dienes and a tandem isomerization–6π-electron electrocyclic ring-closure.

Screening through various thermal conditions [entries 1–7 in Table 1] including several solvents distinctly revealed that isomerization of achiral allenamide **1** was the most effective at 115 °C in CH_3CN [sealed tube], leading to 2-amido-diene **2**[18] in 78% isolated yield and 16:1 ratio [entry 4] in favor of the *E*-geometry [assigned later]. While there appears to be a solvent effect on the *E/Z* ratio [entries 5–7], we found that with the exception of $HNTf_2$ and PTSA [entries 8–9], a range of Brønsted acids were equally effective and more facile at RT in providing 2-amido-diene **2** with excellent *E/Z* ratio [entries 10–13].

Generality of this α-isomerization could be established as shown in Table 2. Key features are: (1) An array of chiral allenamides **5–7** could be employed to construct *de novo* 2-amido-dienes **8–10** with comparable yields and *E/Z* ratios under thermal [higher temperature at 135 °C] or acidic conditions [entries 2–11]; (2) unsubstituted 2-amido-dienes **8d** and **9c** could also be accessed in good yields [see R = H in entries 7 and 9]; (3) allenamide **11** containing an acyclic amide is also feasible for the isomerization; and (4) a single-crystal X-ray structure of **10b** was attained to unambiguously assign the *E*-configuration [Figure 1].

Although our main interest resides in identifying a useful protocol for synthesizing 2-amido-dienes given its greater scarcity,[10–12,19,20] we examined isomerizations of allenamides from the γ-position en route to more well-known 1-amido-dienes.[21] As shown in Table 3, isomerizations of two types of γ-substituted allenamides, those with a cyclohexylidene group [see **13–16** in entries 1–13], and those with an isopropylidene group [see **17–19** in entries 14–19] led to 1-amido-dienes **20–26** exclusively as *E*-enamides [assigned based on the *trans*-olefinic proton coupling constant].

A keen observation here for the γ-isomerization is that acidic conditions appear to be more effective in general with the exception of **17** [entry 15]. In addition, thermal isomerizations at the γ-position required higher temperatures and/or longer reaction times than those of α-isomerizations. This difference prompted us to explore a possible regioselective isomerization. As shown in Scheme 2, when heating allenamides **27a** and **27b**, containing both α- and γ-substituents, at 135 °C in CH_3CN, isomerizations occurred exclusively at the α-position, leading to 2-amido-dienes **28a** and **28b**[22] in 71% and 94% yields, respectively, all in favor of the *E*-enamide [assigned by NOE[18]]. Isomerization of allenamide **27c** took place at RT when in contact with silica gel but again α-isomerization was favored. This regioselective isomerization are both mechanistically intriguing[23] and should be great synthetic value in constructing highly substituted 2-amido-dienes.

The *E*-selectivity[23] attained from α-isomerization provides an excellent platform for the following important pericyclic transformation. As shown in Scheme 3, isomerization of α-allylated allenamide **29** under acidic conditions afforded 3-amido-triene **30** in 86% yield. With the *E*-selectivity, triene **30** is perfectly suited for a thermal 6π-electron electrocyclic ring-closure[24] to give cyclic diene **31**. Although only in 35% yield,[25] examples of cyclic 2-amido-dienes such as **31** are more rare.[26] Allenamide **32a** provided a good example of synthesizing cyclic 2-amido-diene **34a** via acid-promoted α-isomerization followed by ring-closure. Allenamide **32b** demonstrated that the thermal isomerization could be arrested with the *gem*-dimethyl group in triene **33b** impeding the ring-closure. Unfortunatedly, attempted ring-closure of **32b** at 200 °C led to an unidentified product instead of **34b**.

At last, this process could be rendered in tandem under thermal conditions to access cyclic 2-amido-dienes **34a**, **37**, and **38** in good overall yields directly from respective allenamides **32a**, **35**, and **36** [Scheme 4]. It is noteworthy that these 6π-electron pericyclic ring-closures mostly took place at 135 °C, which implies an accelerated process. This feature is consistent with related ring-closures of 1,3,5-hexatrienes bearing a C3-donating group.[27,28]

We have described here a regio- and stereoselective isomerization of allenamides, leading to preparations of *de novo* 2-amido-dienes and a tandem isomerization–6π-electron electrocyclic ring-closure. Studies involving applications of these dienes and this new tandem process as well as mechanistic understanding of this allene-isomerization are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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22. There appears to be ~% of 1-amido-diene from γ-isomerization.

23. Without detailed studies, a rationale for lowering of the thermal activation barrier of 1,3-H-shift is the stabilization of the bi-radical intermediate provided by the nitrogen atom, assuming a radical intermediate is considered electron deficient. Based on the this model, this stabilization is direct when isomerizations take place at the α-position [see **i**], and "vinylogous" for isomerizations at the γ-position [see **ii**]. Thus, thermal isomerizations at the α-position were faster than at the γ-position. As one reviewer suggested, it is also possible that the nitrogen atom mediates a polarized transition sate in which an increasing charge density at the β-carbon could develop, leading to an *N*-acyl iminium ion-like character with the migrating hydrogen behaving more like a proton. This charged transition state instead of a neutral one should possess a lower thermal activation barrier for the 1,3-H-shift. Finally, a rationale for the *E*-selectivity from the thermal α-isomerization is that the *pro-Z*-TS experiences a greater allylic strain than the *pro-E*-TS during the 1,3-H-shift, although we cannot rule out equilibration from *Z*- to *E*-enamide after the initial isomerization.

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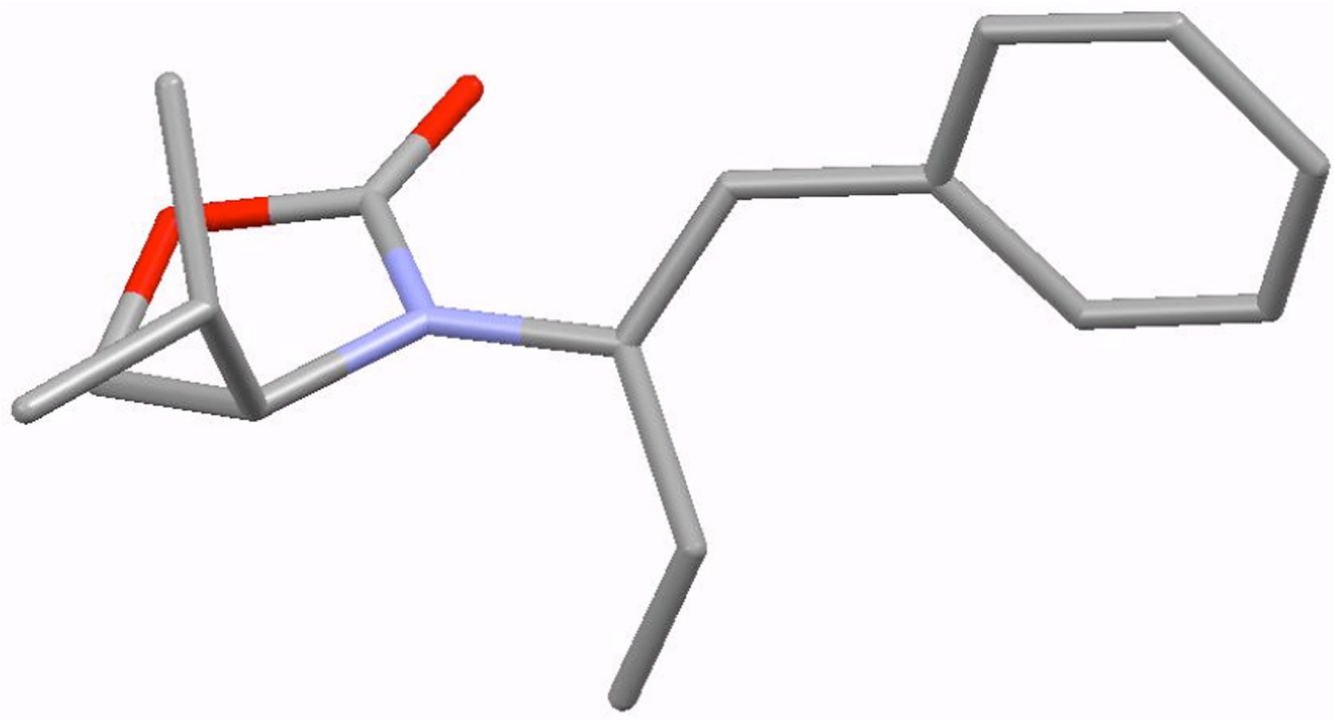
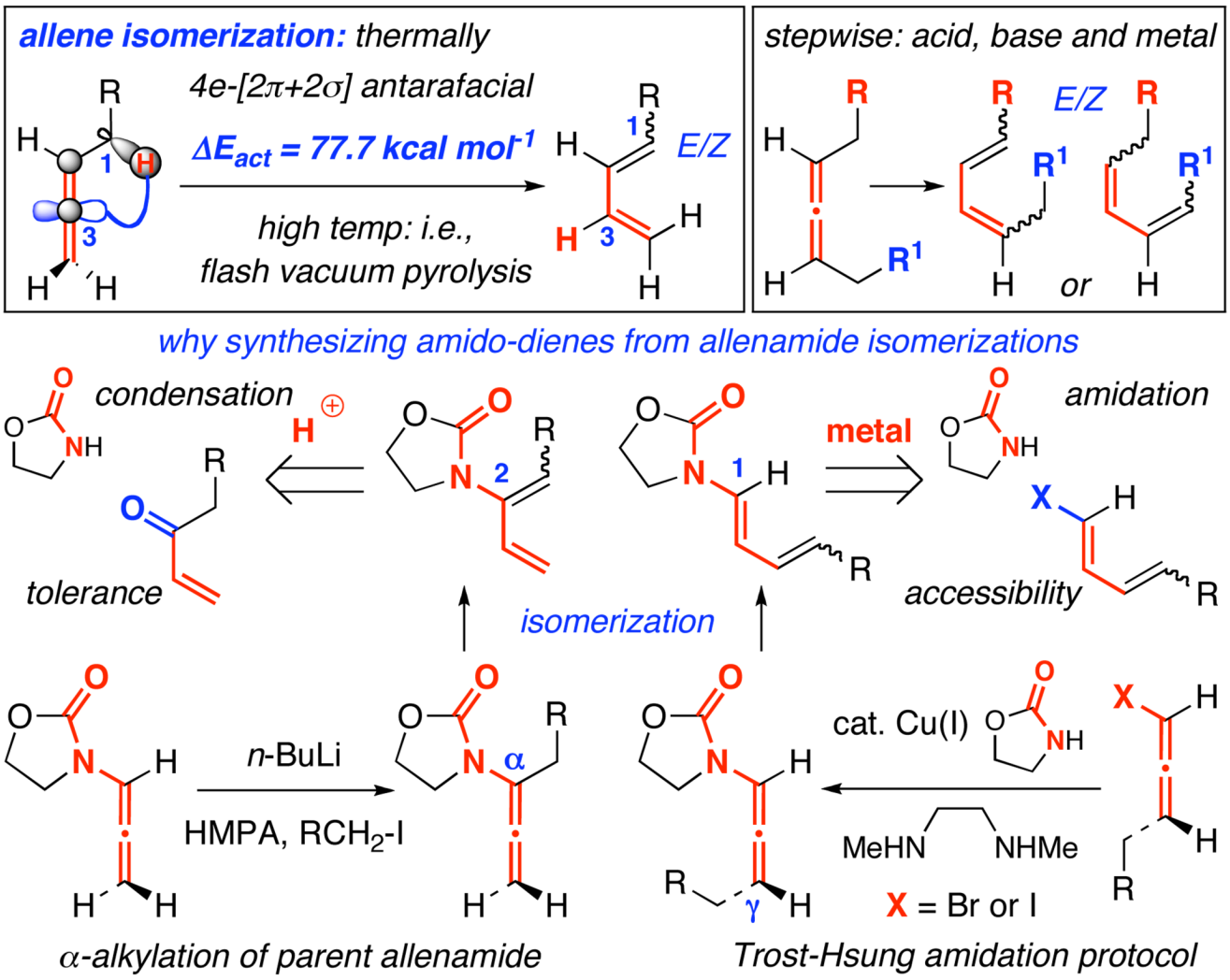
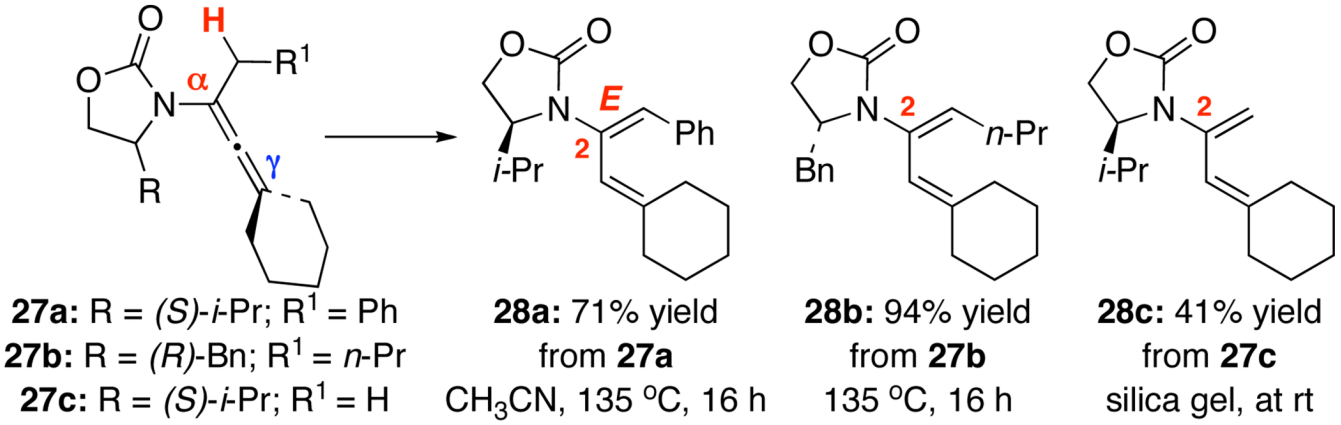


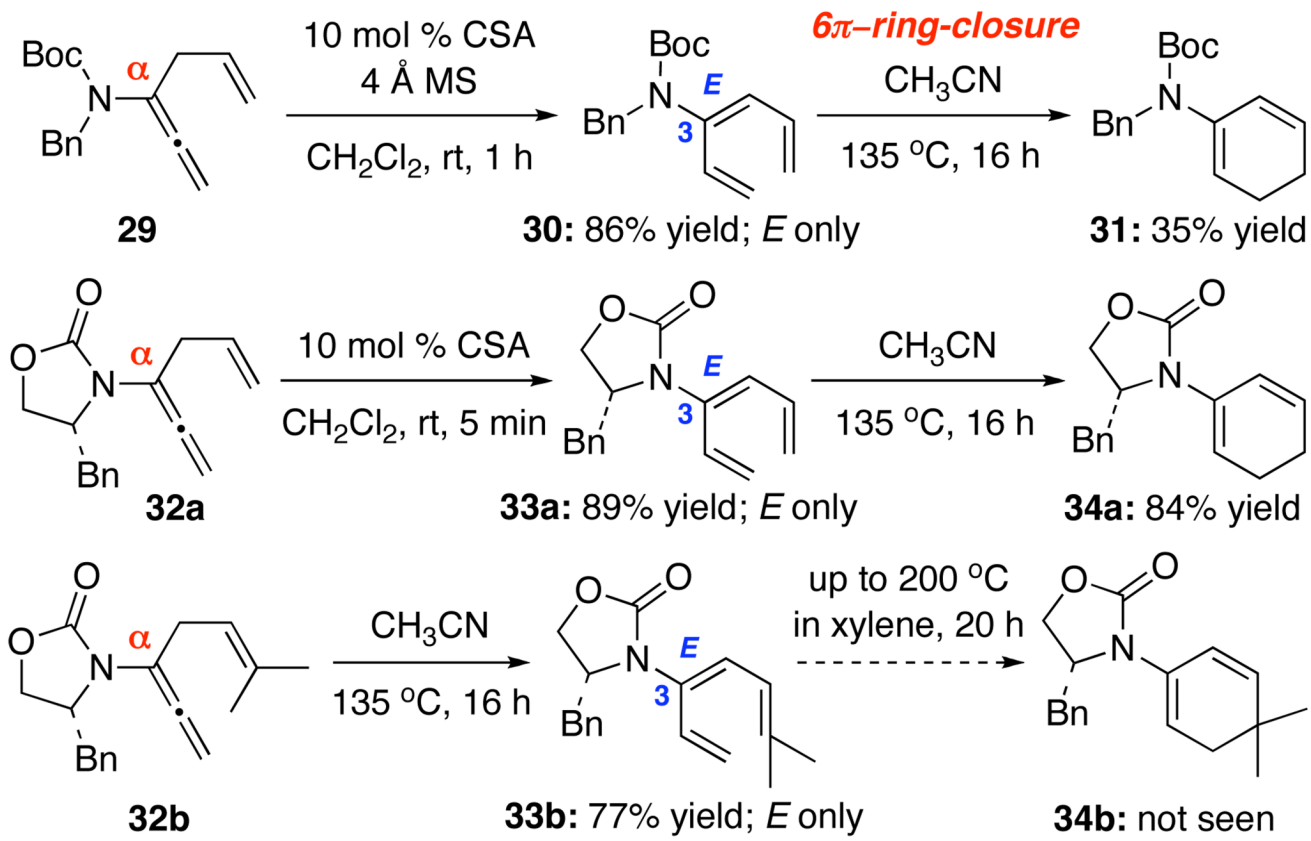
Figure 1.
X-Ray Structure of 2-Amido-Diene **10b**.



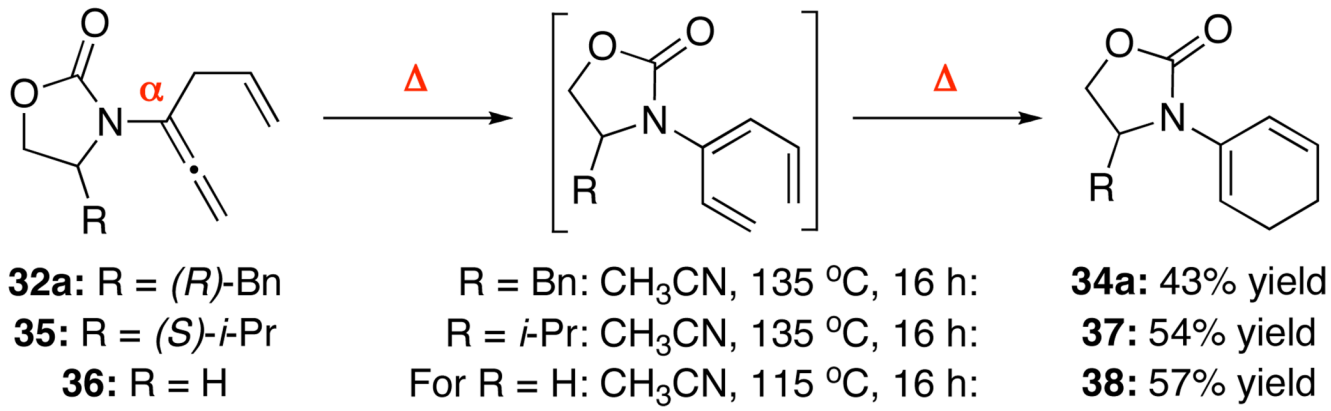
Scheme 1.
Allene Isomerizations.



Scheme 2.
Regioselective α-Isomerizations.



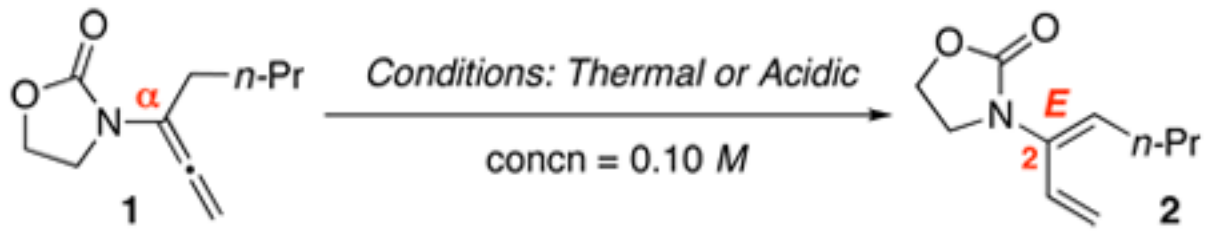
Scheme 3.
3-Amido-Trienes and Pericyclic Ring-Closure.



Scheme 4.
A Tandem α-Isomerization–Pericyclic Ring-Closure.

Table 1

Thermal vs. Acidic Conditions.



entry	solvent	acid [10 mol %]	temp [°C]	time [h]	yield [%][a,b]	*E*:*Z*[c]
1	CH_3CN	-	25	16	0	-[d]
2	CH_3CN	-	55	16	51	≥20:1
3	CH_3CN	-	85	16	88	≥20:1
4	**CH_3CN**	**-**	**115**	**16**	**91 [78]**	**16:1**
5	THF	-	115	16	51	9:1
6	$ClCH_2CH_2Cl$	-	115	16	79	7:1
7	Tol	-	150	16	55	4:1
8	CH_2Cl_2	$HNTf_2$	25	5 min	0	-[e]
9	CH_2Cl_2	PTSA	25	1	66	2:1
10	CH_2Cl_2	4-NO_2PhCO_2H	25	16	81	15;1
11	CH_2Cl_2	$PhCO_2H$	25	16	85 [55]	18:1
12	CH_2Cl_2	PPTS	25	16	77	15:1
13	**CH_2Cl_2**	**CSA**	**25**	**10 min**	**95 [74]**	**18:1**

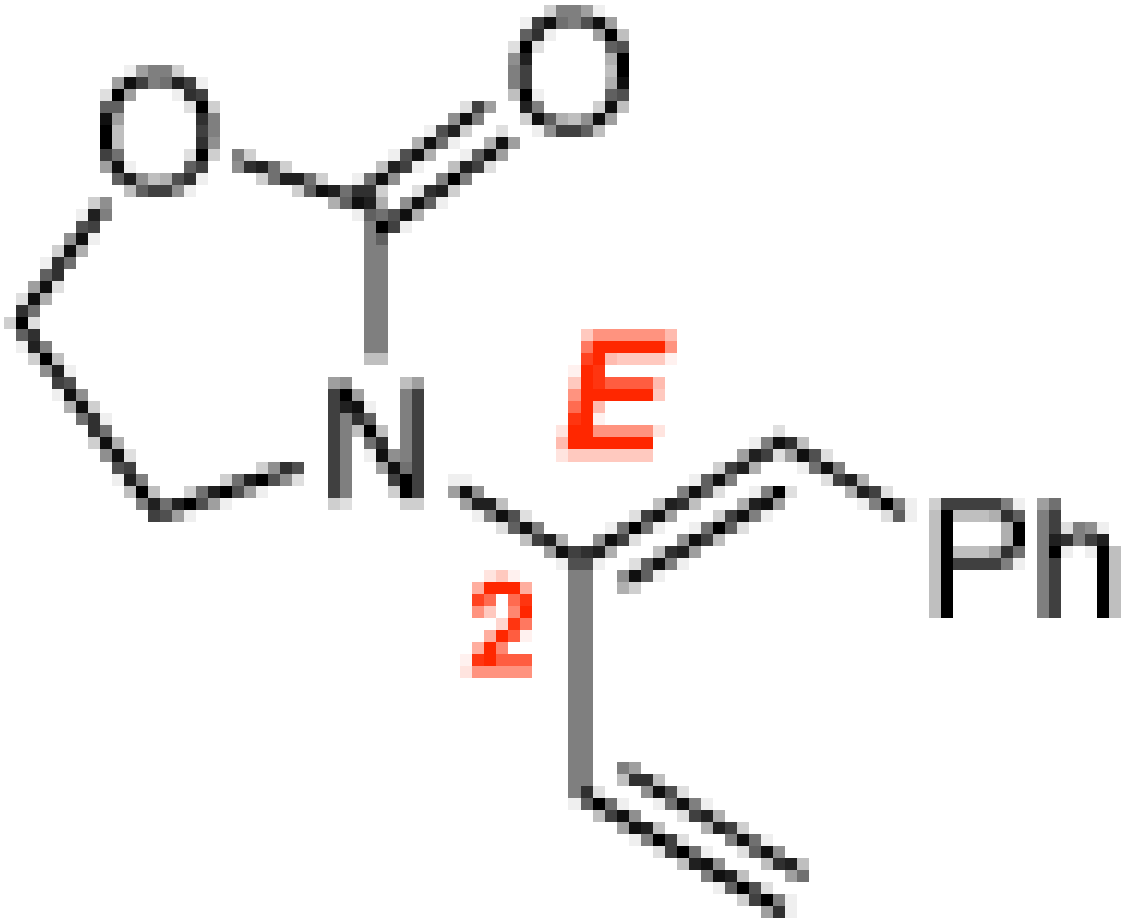
[a] NMR yields.

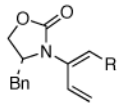
[b] Isolated yields in the bracket.

[c] Determined by ^{1}H-NMR.

[d] Allenamide **1** was recovered.

[e] Allenamide **1** decomposed.

	conditions [time][a]	dienes	yield [%][b]		E:Z[c]
3	115 °C, 16 h		**4**	71	6:1
5a: R = *n*-Pr	135 °C, 6 h		**8a**	77	≥20:1

	conditions [time][a]	dienes		yield [%][b]		E:Z[c]
5a: R = *n*-Pr	CSA, 4 h[d]		**8a**	87		≥20:1
5b: R = Ph	135 °C, 16 h		**8b**	74		≥20:1
5b: R = Ph	CSA, 2 h		**8b**	83		≥20:1
5c: R = ^{2}Nap	135 °C, 16 h[e]		**8c**	73		≥50:1

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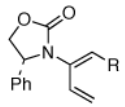
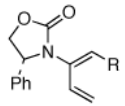
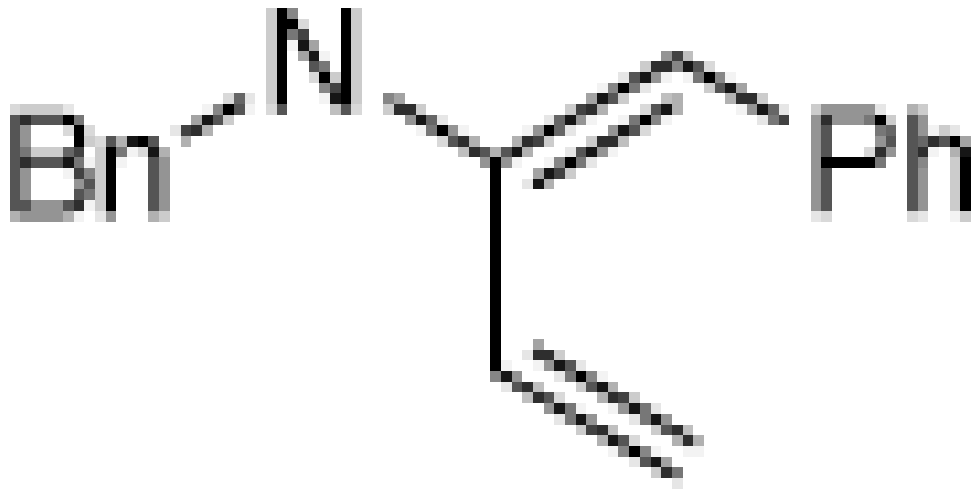
	conditions [time][a]	dienes	yield [%][b]		E:Z[c]
5d: R = H	135 °C, 16 h		**8d**	69	-
6a: R = *n*-Pr	CSA, 10 min		**9a**	82	≥50:1
6b: R = Ph	CSA, 10 min		**9b**	76	≥50:1
6c: R = H	135 °C, 16 h		**9c**	69	-
7a: R = *n*-Pr	135 °C, 16 h		**10a**	62	≥50:1
7b: R = Ph	135 °C, 16 h		**10b**	82	≥50:1

	conditions [time][a]	dienes	yield [%][b]		E:Z[c]
11	135 °C, 16 h		**12**	45	≥20:1
11	CSA,[f] 2 h		**12**	61	≥20:1

tions, *concn* = 0.10 *M*.

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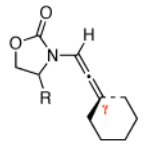
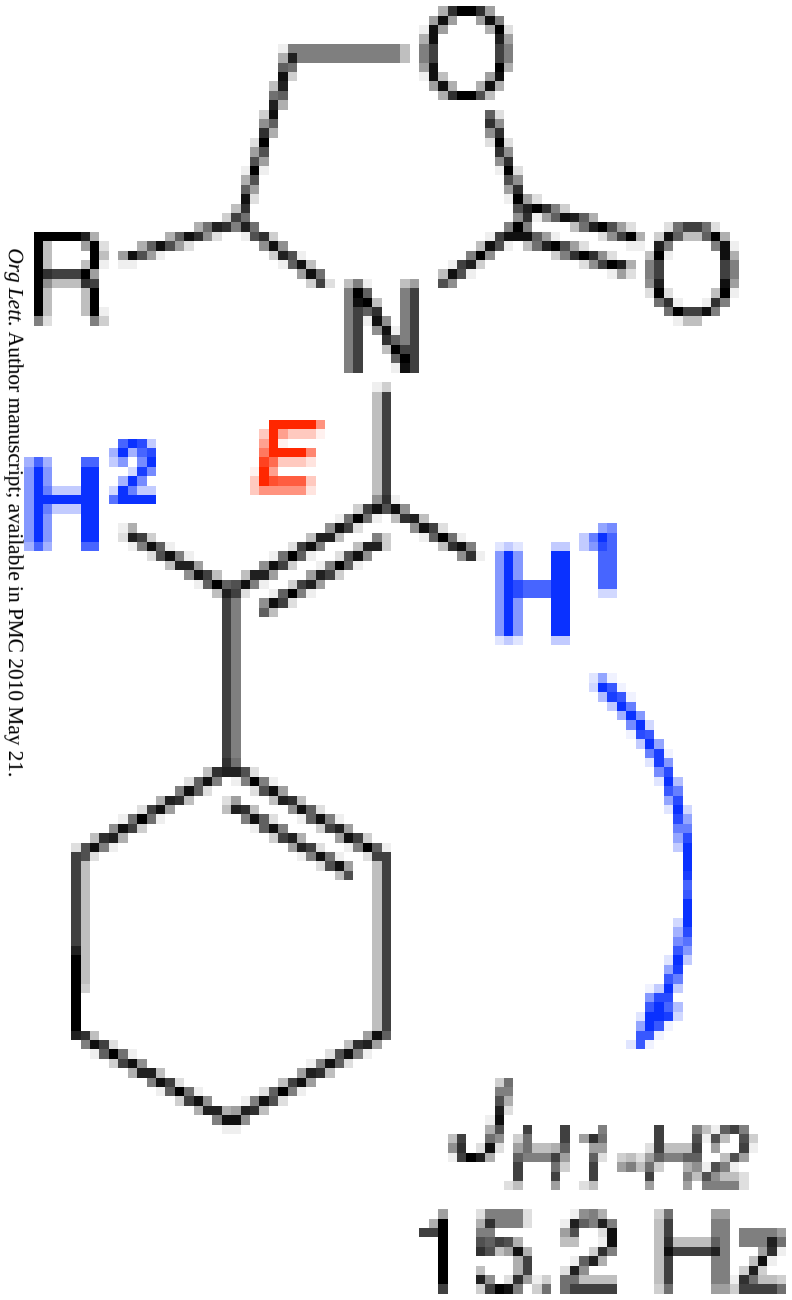
f_{4} Å MS was used.

Table 3

Isomerization of Allenamides at the γ-Position.

allenamides	conditions [time][a]	dienes	yield [%][b,c]
13a: R = (*R*)-Ph	135 °C, 16 h		**20a** ≤10[d]

allenamides	conditions [time][a]	dienes	yield [%][b,c]
	PTSA, 10 min		95
	CSA, 10 min		89
13b: R = (*R*)-Bn	135 °C, 16 h	**20b**	25[e]
	PTSA, 5 min		96
	CSA, 10 min		95
13c: R = *(S)-i*-Pr	135 °C, 16 he	**20c**	50[f]



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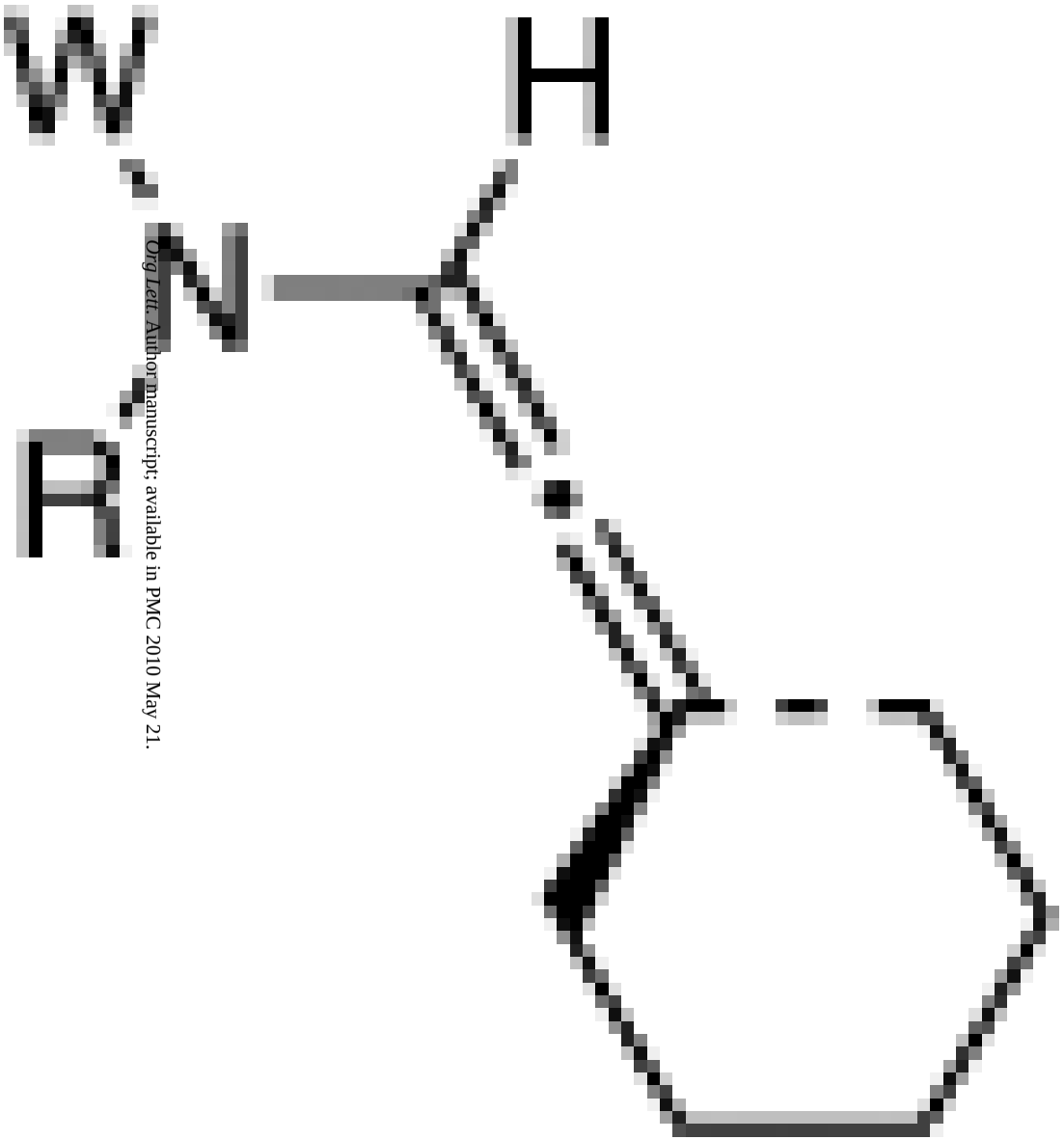
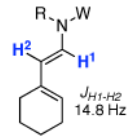
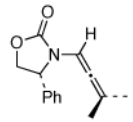
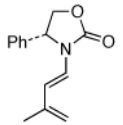
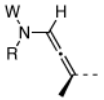
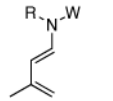
allenamides	conditions [time][a]	dienes	yield [%][b,c]
	PTSA, 10 min		88

allenamides	conditions [time][a]	dienes	yield [%][b,c]	
				
14: W = Ac; R = Ph	175 °C,[g] 24 h		**21**	95
	CSA,[h] 10 min			90
15: W = Ts; R = Bn	175 °C,[g] 24 h		**22**	96
	CSA,[h] 10 min			97
16: W = $PhCH_2CH_2CO$ R = Ph	175 °C,[g] 24 h		**23**	98

allenamides		conditions [time][a]	dienes		yield [%][b,c]
	**17**	135 °C, 16 h		**24**	95
	17	PTSA, 5 min		**24**	-[i]
	**18:** W = Ac; R = Ph	175 °C,[g] 24 h		**25**	46[j]
		CSA,[h] 10 min			97
	19: W = Ts; R = Bn	135 °C, 48 h		**26**	77[j]
		CSA,[h] 10 min			99

rwise noted, CH_3CN was the solvent for thermal conditions, and CH_2Cl_2 was the solvent when using 10 mol % of PTSA or CSA at rt. In all reactions, *concn* was 0.10 *M*.

lds.

ners were observed.

g allenamide recovered.

g allenamide recovered.

g allenamide recovered.

s the solvent.

s used.

ion.

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