ORGANIC LETTERS

2011
Vol. 13, No. 12
3114–3117

Oppolzer-Type Intramolecular Diels–Alder Cycloadditions via Isomerizations of Allenamides

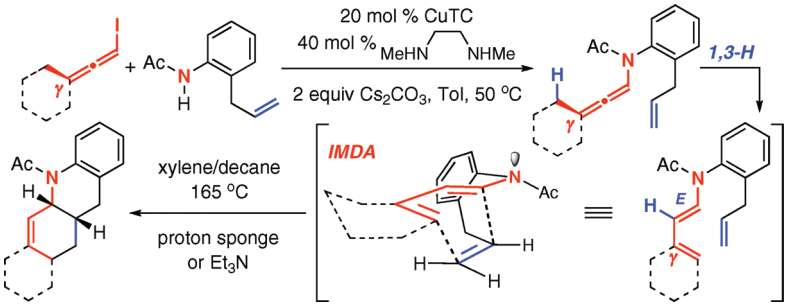
John B. Feltenberger and Richard P. Hsung*

Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53705, United States

rhsung@wisc.edu

Received April 17, 2011

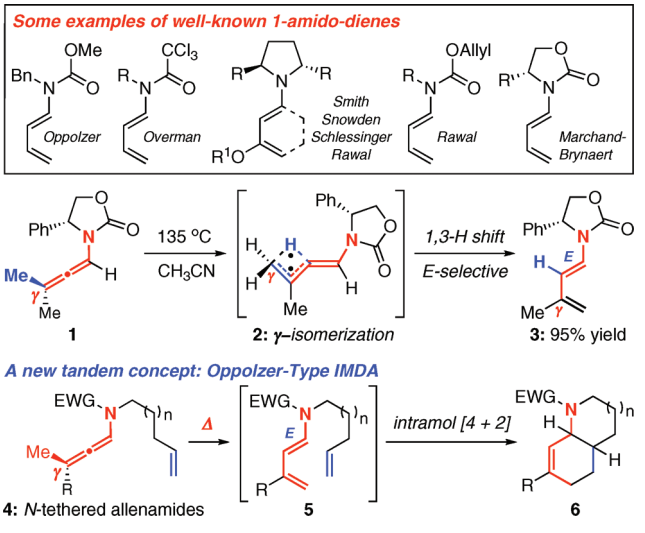
ABSTRACT



A new approach to Oppolzer's intramolecular Diels–Alder cycloaddition (IMDA) through γ-isomerization of readily available *N*-tethered allenamides is described. These IMDA reactions are carried out in tandem with the allenamide isomerization or 1,3-H shift, leading to complex nitrogen heterocycles in a highly stereoselective manner.

Intermolecular Diels–Alder cycloadditions of 1-amino- or 1-amido-dienes[1−7] have proven to be a powerful reaction manifold, with some notable examples shown in Scheme 1. Although Oppolzer[8,9] had elegantly demonstrated the concept of *N*-tethered 1-amido-dienes in intramolecular Diels–Alder cycloadditions (IMDA),[10] relative to the intermolecular pursuit, it has shown limited applications

Scheme 1. Oppolzer's IMDA via Allenamide Isomerization



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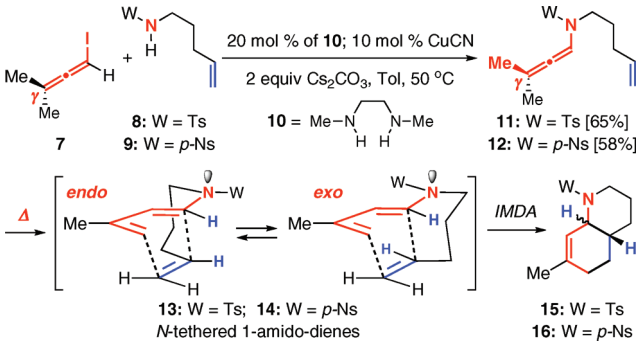
10.1021/ol2010227
Published on Web 05/25/2011

in the past 40 years in part due to a lack of efficient synthetic access to these cycloaddition precursors.[10,11] We recently reported[12] that γ-isomerizations of allenamides **1** provide a facile entry to 1-amido-dienes **3** via a stereoselective 1,3-H shift (Scheme 1).[13] This finding provokes a unique synthetic design in which the allenamide isomerization could be rendered in tandem with the Oppolzer-type intramolecular Diels–Alder cycloaddition when using *N*-tethered allenamides **4**. If successful (**4** → **5** → **6**), such an endeavor would allow rapid assembly of structural complexity from simple allenamides and further underscores the significance of developing chemistry of allenamides.[14–16] We communicate here an Oppolzer-type IMDA through γ-isomerizations of allenamides.

Scheme 2. Facile Assembly of *N*-Tethered Allenamides



While the general plan is laid out concisely in Scheme 2 with allenamides **11** and **12**[17] readily attainable through amidative cross-coupling[1f,18] of allenyl iodide **7** with respective amides **8** and **9**, developing an effective γ-isomerization in conjunction with Oppolzer's IMDA was not trivial; a wide range of conditions had to be examined (Table 1). While the modest yields attained under a number of conditions (entries 2–8) could still be considered useful given the context of constructing multiple bonds and stereocenters in a tandem sequence, ultimately it appeared that a base, optimally being a proton sponge (entry 11) or Et_3N (entry 14), was needed to avoid significant hydrolysis

Table 1. Tandem γ-Isomerization–Oppolzer-Type IMDA

entry	W =	solvent[a]	additive [equiv]	temp [°C]	time [h]	yield [%][b]
1	**11:** Ts	toluene	-	135	18	trace[c]
2	**11:** Ts	toluene	-	170	26	13[d]
3	**12:** *p*-Ns	xylene	-	150	40	42
4	**12:** *p*-Ns	xylene	-	180	19	33
5	**12:** *p*-Ns	decane	-	180	15	25
6	**12:** *p*-Ns	1,2-DiClPh	-	165	24	33
7	**12:** *p*-Ns	Ph_2O	-	165	24	32
8	**12:** *p*-Ns	xyl/decane	-	165	24	38
9	**11:** Ts	toluene	BSA [0.3-5]	165	24	-[e]
10	**12:** *p*-Ns	xyl/decane	BSA [3]	165	24	-[e]
11	**12:** *p*-Ns	xyl/decane	proton sponge [3]	165	24	77
12	**12:** *p*-Ns	xyl/decane	1-Me-imidazole [3]	165	24	63
13	**11:** Ts	xyl/decane	Et_3N [3]	165	24	34
14	**12:** *p*-Ns	xyl/decane	Et_3N [3]	165	24	76
15	**12:** *p*-Ns	xyl/decane	DBU [3]	165	24	trace[f]
16	**12:** *p*-Ns	xyl/decane	DABCO [3]	165	24	trace[f]
17	**12:** *p*-Ns	xyl/decane	Cs_2CO_3 [3]	165	24	48
18	**12:** *p*-Ns	xyl/decane	K_2CO_3 [3]	165	24	~ 5[f]
19	**12:** *p*-Ns	xyl/decane	4Å MS [3]	165	24	~ 5[f]
20	**12:** *p*-Ns	xyl/decane	Na_2SO_4 [3]	165	24	~ 5[f]

[a] All reactions were run in screw-cap vials with Teflon-coated caps. Concentration = 0.05 M, except for entries 1–3 and 10 where concentration = 0.02 M. [b] Isolated yields for **15** or **16**. [c] The only product was *N*-tethered 1-amido-diene **13** in 78% yield. [d] The respective secondary amide was isolated in 15% yield as a result of hydrolysis along with 26% of **13**. [e] A complex mixture. [f] Mostly decomposition of **12**.

of starting allenamides. Other amine bases, inorganic bases, or drying agents screened were not effective (entries 15–20).

In addition, a *p*-nosyl substituent on the nitrogen atom provided higher yield of the respective cycloadduct **16** (entry 14), relative to cycloadduct **15** containing an *N*-Ts group (entry 13). Diastereoselectivity or the *endo*:*exo* ratio for **16** (dr = 10:1) was also slightly higher than that of **15** (dr = 8:1). Relative stereochemistry of the major isomer of

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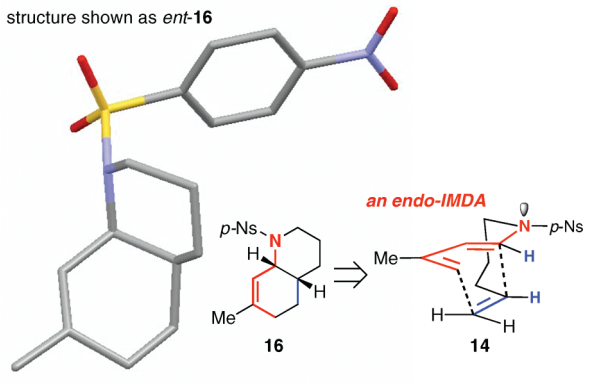
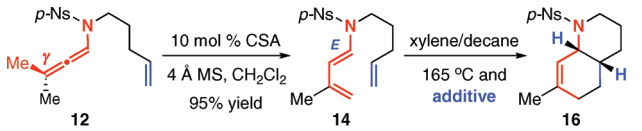


Figure 1. X-ray structure of **16**.

16 was unambiguously assigned using single crystal X-ray structure (Figure 1), thereby suggesting a favored *endo*-transition state with respect to the carbon tethering.

Scheme 3. Sequential Pursuit versus Tandem Process



A quick comparison was drawn through pursuing this Oppolzer-type IMDA sequentially in conjunction with the γ-isomerization of allenamides. As shown in Scheme 3, acid-catalyzed isomerization of allenamide **12** gave *N*-tethered 1-amido diene **14** in near quantitative yield. The ensuing cycloaddition using either Et_3N or a proton sponge as the additive led to cycloadduct **16** with a combined yield for either condition very comparable to those attained in a tandem manner (in italics).

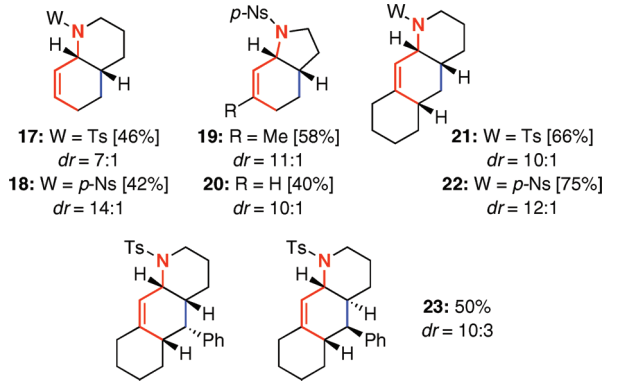
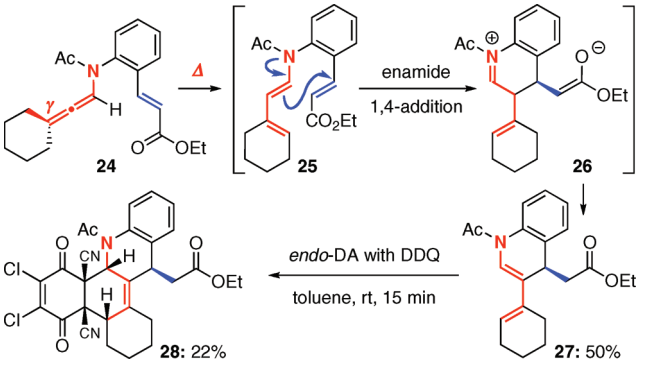


Figure 2. Tandem γ-isomerization–Oppolzer-type IMDA. All reactions were run for 40–48 h in screw-cap vials with Teflon-coated caps at 165–175 °C using the xylene/decane mixed solvent system and 3.0 equiv Et_3N as additive. Cycloaddition for preparing **23** was run at 210 °C. The diastereomeric ratios were determined using ^1H and/or ^{13}C NMR.

Having established the feasibility, various examples could be readily produced including tricycles **21**–**23** (see product Figure 2). In general, the *p*-nosyl substitution gave better yields, and both stereoselectivity and overall yields are in the synthetically useful range and could be considered excellent in the context of constructing multiple bonds and stereocenters. It is noteworthy that additional substitutions on the olefin such as a Ph group could be included, leading to cycloadduct **23** with an *endo*:*exo* ratio of 10:3 (the *endo* isomer was assigned using NOE experiments). In addition, the original *cis* configuration of the olefin was preserved during the cycloaddition.

Scheme 4. Unexpected Enamide 1,4-Addition



(15) Also see: (a) Lohse, A. G.; Hsung, R. P. *Chem.—Eur. J.* **2011**, *17*, 3812. (b) Standen, P. E.; Kimber, M. C. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 645. (c) Deagostino, A.; Prandi, C.; Tabasso, S.; Venturello, P. *Molecules* **2010**, *15*, 2667. (d) For general reviews on allenes, see: Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vols 1 and 2.

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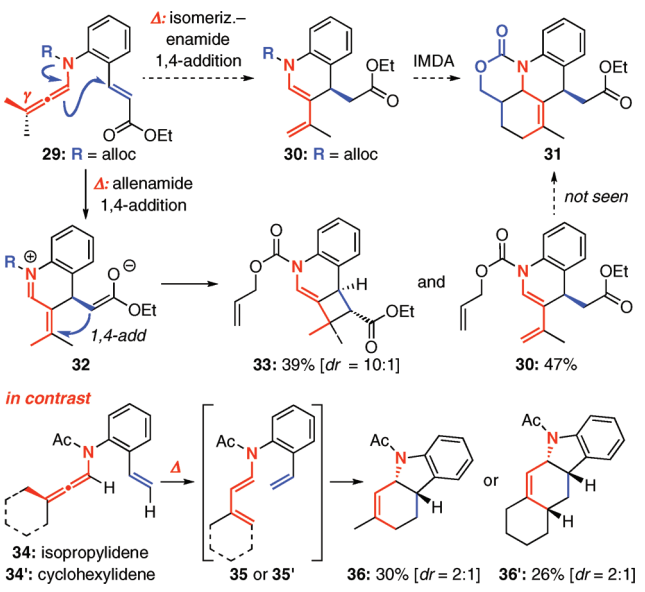
(17) See Supporting Information.

We then turned our attention toward constructing heterocycles with greater complexity. However, when using allenamide **24** containing a cinnamate motif in an attempt to prepare indolines through the tandem γ-isomerization–IMDA sequence, we encountered an unexpected enamide 1,4-addition (see **25**), leading to the formation of amido diene **27** (Scheme 4). This new diene was only fully recognized after we were attempting an aromatization process using DDQ, which led to another Diels–Alder cycloadduct **28**.

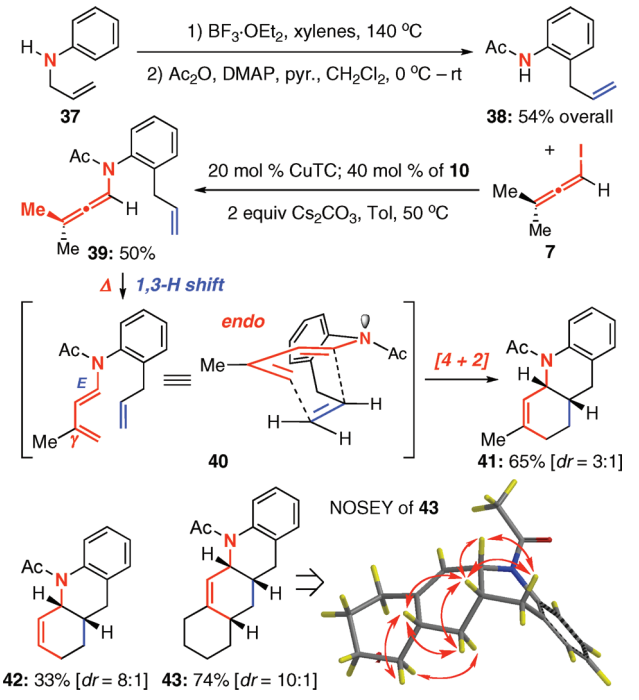
Scheme 5. Assembly of Indolines



Contemplating taking advantage of this new observation we prepared allenamide **29** containing an alloc group with the hope that another IMDA could take place through diene **30** leading to tetracycle **31** (Scheme 5). Surprisingly, we found that 1,4-addition was even occurring prior to the allenamide isomerization, leading to the formation of cyclobutane **33**. Cyclobutane **33** most likely was derived from two consecutive 1,4-additions with the latter involving vinyl iminium ion **32**. On the other hand, although the major product, 1-amido-diene **30** did not undergo further IMDA to give the anticipated tetracyclic quinoline **31**. Fortuitously, this issue could be circumvented by using allenamide **34** and **34′**, which gave respective indolines **36** and **36′** in modest overall yield through the expected sequence of tandem γ-isomerization–Oppolzer-type IMDA. Unfortunately, the *endo*:*exo* ratios for these cases were not high.

(18) (a) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117. (b) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081. Also see: (c) Persson, A. K. Å; Johnston, E. V.; Bäckvall, J.-E. *Org. Lett.* **2009**, *11*, 3814.

Scheme 6. Rapid Constructions of Quinolines



The power of this tandem sequence can be manifested in the quinoline synthesis. As shown in Scheme 6, a number of quinolines such as **41**–**43** could be accessed rapidly in an efficient manner from simple *N*-allyl-aniline **37** in four steps. These rapid assemblies feature aza-Claisen, copper-catalyzed amidative cross-coupling and tandem γ-isomerization–Oppozler-type intramolecular Diels–Alder cycloaddition. In particular, the tandem sequence is stereoselective for the synthesis of the tetracyclic quinoline **43**, which was isolated in 74% yield with a diastereomeric ratio of 10:1. The major isomer of **43** was concisely assigned using a NOE experiment.

We have described here an Oppolzer-type intramolecular Diels–Alder cycloaddition (IMDA) through γ-isomerization of readily available *N*-tethered allenamides. These IMDA reactions are carried out in tandem with the allenamide isomerization, which consists of a 1,3-H shift, leading to complex nitrogen heterocycles in a highly stereoselective manner. Applications of this new tandem process in alkaloid synthesis are underway.

Acknowledgment. Authors thank NIH (GM066055) for support and Dr. Victor Young, University of Minnesota for X-ray structural analysis.

Supporting Information Available. Experimental procedure sand NMR spectra, characterizations, and X-ray structural files. This material is available free of charge via the Internet at http://pubs.acs.org.