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First Stereoselective Inverse Demand [4 + 2] Cycloaddition Reactions of Novel Chiral Allenamides with Heterodienes. Preparation of Highly Functionalized 2-Arylpyranyl Heterocycles

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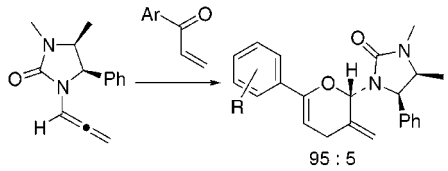
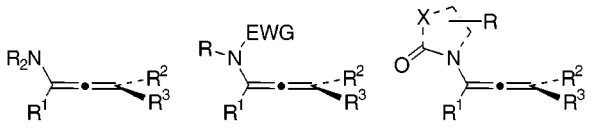
ABSTRACT



The first stereoselective inverse demand [4 + 2] cycloaddition reactions of chiral allenamides with heterodienes are described here. These reactions lead to stereoselective synthesis of highly functionalized pyranyl heterocycles. A mechanistic model is also proposed here based on the stereochemical assignment and comparisons of stereoselectivities obtained from various chiral allenamides.

Allenes are among the most important building blocks in organic synthesis, serving critical roles in a diverse array of modern synthetic methods.[1] However, an important subgroup of allenes, allenamines, has received limited attention in synthetic applications [Figure 1].[1] This lack of attention could be attributed to the difficulty in preparation and handling of allenamines due to their high reactivity and sensitivity toward hydrolysis. Because of our interest in developing methodologies for constructing heterocycles,[2,3] we have been exploring syntheses and reactivities of a new class of allenamines that can present superior stability to the traditional allenamines without compromising any reactivity.[3a] Specifically, they are



allenamines stabilized allenamines allenamides

Figure 1.

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(1) For reviews, see: (a) Saalfrank, R. W.; Lurz, C. J. In *Methoden Der Organischen Chemie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; p 3093. (b) Schuster, H. E.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley and Sons: New York, 1984.

(2) (a) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904. (b) Hsung, R. P. *Heterocycles* **1998**, *48*, 421. (c) Granum, K. G.; Merkel, G.; Mulder, J. A.; Debbins, S. A.; Hsung, R. P. *Tetrahedron Lett.* **1998**, 9597. (d) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690. (e) Degen, S. J.; Mueller, K. L.; Shen, H. C.; Mulder, J. A.; Golding, G. M.; Wei, L.-L.; Zificsak, C. A.; Hsung, R. P. *Bioorg. Med. Chem. Lett.* **1999**, 973. (f) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509. (g) Douglas C. J.; Sklenicka, H.; Shen, H. C.; Golding, G. M.; Mathias, D. S.; Degen, S. J.; Morgan, C. D.; Shih, R. A.; Mueller, K. L.; Seurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, 13683. (h) Hsung, R. P.; Zificsak, C.; Wei, L.-L.; Zehnder, L.; Park, F.; Kim, M.; Tran, M. *J. Org. Chem.* **1999**, *64*, 8736.

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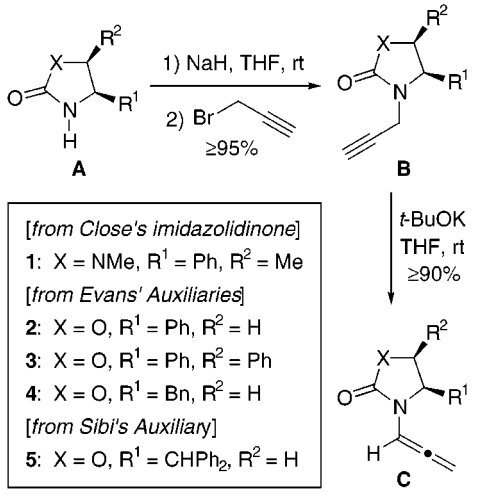
allenamides in which the nitrogen atom contains electron-withdrawing groups. Our design of allenamides would feature either an imidazolidinone or oxazolidinone moiety, thereby providing a practical entry that could lead to chiral allenamides [Figure 1]. While allenamines are the least studied among heteroatom-substituted allenes, studies of allenamides are even more rare.[1] Since their first preparations[4,5] 20−30 years ago, the most common electron deficient allenamines are those in which the nitrogen atom is part of a heteroaromatic system prepared for medicinal purposes.[6,7] Some examples of palladium-catalyzed cross-couplings,[8] cyclizations,[9] and [2 + 2] cycloaddition reactions[10] using electron deficient allenamines have been reported. We recently reported synthesis of various new allenamides and explored their synthetic potential.[3a] We report here the first examples of stereoselective inverse demand [4 + 2] cycloaddition reactions of chiral allenamides with heterodienes.

The chiral allenamides could be readily prepared using a base-induced isomerization. As shown in Scheme 1, a variety

Scheme 1



of chiral allenamides were obtained in high yields over two steps starting from Close's chiral imidazolidinone [leading to **1**],[11] Evans' oxazolidinone auxiliaries [leading to **2**−**4**],[12] or Sibi's dibenzylidene-substituted oxazolidinone [leading to **5**].[13] Propargylations were carried out in quantitative yields using NaH and propargyl bromide. Freshly prepared *t*-BuOK was used to induce the isomerization in anhydrous THF at room temperature, leading to the desired chiral allenamides **1**−**5** in greater than 90% yields.[14] Chiral allenamides **1**−**5**[15] may be obtained in gram quantities as crystalline solids that can be handled with ease. Purification of these chiral allenamides simply involved filtration through Celite or alumina.

Having prepared these chiral allenamides, we proceeded to examine their reactivity as well as level of stereoinduction in inverse demand [4 + 2] cycloaddition reactions with heterodienes. Chiral allenamide **1** containing the imidazolidinone group was found to be reactive toward a diverse array of heterodienes. The results are summarized in Table 1. Most of these reactions were carried out at 80 °C leading to pyranyl heterocycles **6**, **7**, and **17**−**25**[15] in good yields as well as high enantioselectivities. The more polar CH_3CN appears to be a better solvent than 1,2-dicholorethane given the reaction time [entries 1−4]. This suggests a stepwise sequence involving ionic intermediates for the cycloaddition.[3a,16] The aryl vinyl ketones **9**−**14** were more reactive [entries 5−11] than acrolein [entries 1 and 2], methyl vinyl ketone [entries 3 and 4], and other alkyl vinyl ketones [entries 12 and 13] as indicated by the overall shorter reaction durations and superior yields. These aryl ketones led to preparations of an array of highly functionalized 2-arylpyranyl heterocycles **18**−**23**. Heterodienes **8** and **12** appeared to be the most reactive toward **1** [entries 5 and 9], while the heterodiene **15** appears to be the least reactive.

Reactions of chiral allenamide **1** with alkyl and aryl vinyl ketones also appear to provide the best stereoselectivity, and for heterodienes **12** and **13**, only one isomer was observed [Table 1, entries 9 and 10]. The stereochemistry was assigned by X-ray diffraction of a single crystal of pyran **24**, and a consistent ^{1}H NMR correlation allowed stereochemical assignment of all other cycloadducts.[17] The X-ray crystal structure also indicates that the chiral imidazolidinoe group is in the pseudoaxial position.

Control experiments showed that these stereochemical ratios are not affected by the reaction conditions. When pyran **23** containing the enriched minor isomer [an 18:82 ratio of major:minor] was heated at 80 °C in CD_3CN and monitored by ^{1}H NMR for 12 h, the integrity of the initial diastereomeric ratio was not eroded and the final ratio was 13:87 [major:minor] without apparent loss of material. It is noteworthy that allenamide **1** is more stable than any existing allenamine because allenamines tend to polymerize at the temperature at which these reactions were carried out.[1a]

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(5) Overman, L. E.; Marlowe, C. K.; Clizbe, L. A. *Tetrahedron Lett.* **1979**, 599.
(6) (a) Rádl, S.; Kovárová, L. *Collect. Czech. Chem. Commun.* **1991**, *56*, 2413. (b) Reisch, J.; Salehi- Artimani, R. A. *J. Heterocycl. Chem.* **1989**, *26*, 1803.
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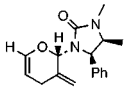
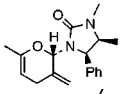
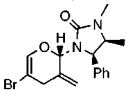
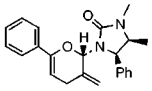
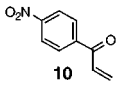
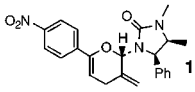
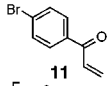
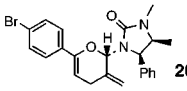
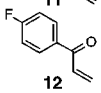
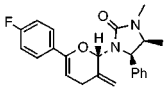
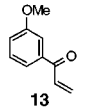
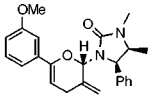
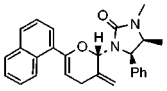
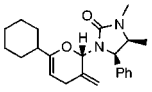
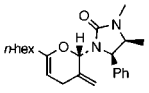
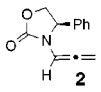
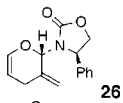
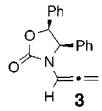
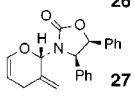
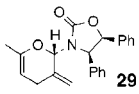
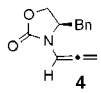
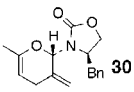
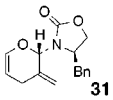
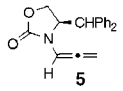
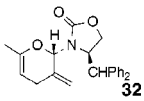
(10) Kimura, M.; Horino, Y.; Wakamiya, Y.; Okajima, T.; Tamaru, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9, 10869 and references therein.
(11) Close, W. J. *J. Org. Chem.* **1950**, *15*, 1131.
(12) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77.
(13) Sibi's dibenzylidene-substituted oxazolidinone can be purchased from Aldrich. For synthesis, see: (a) Sibi, M. P.; Deshpande, P. K.; Ji, J. G. *Tetrahedron Lett.* **1995**, 8965. (b) Sibi, M. P.; Ji, J. G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190. (c) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.
(14) For another example of this isomerization method, see: Pourcelot, G.; Cadiot, P.; Georgoulis, C. *Tetrahedron* **1982**, *38*, 2123.
(15) All new compounds were identified and characterized by ^{1}H NMR, ^{13}C NMR, FTIR, $[\alpha]^{20}_D$, and MS.
(16) Klop, W.; Klusener, P. A. A.; Brandsma, L. *Recl. J. R. Neth. Chem. Soc.* **1984**, *103*, 85.
(17) For all cycloadducts, chemical shifts of the anomeric proton for major isomers are consistently 0.18−0.40 ppm higher than those from minor isomers.

Table 1. Reactions of the Chiral Allenamide **1** with Heterodienes

entry	heterodienes[a]	time[b]	products	yield[c]	*d.r.*[d]
1		5 h	 **6**	65 %	87 : 13
2		15[e]		70	85 : 15
3		7	 **7**	57	94 : 6
4		17[e]		55	93 : 7
5	 **8**	12[f]	 **17**	50	84 : 16
6	 **9**	18	 **18**	63	95 : 5
7	 **10**	12	 **19**	85	92 : 8
8	 **11**	4	 **20**	65	95 : 5
9	 **12**	2	 **21**	78	≥96 : 4
10	 **13**	4	 **22**	70	≥96 : 4
11	 **14**	17	 **23**	74	94 : 6
12	 **15**	48	 **24**	19	95 : 5
13	 **16**	18	 **25**	50	95 : 5

a) 2.0 equiv of heterodiene was used except for entries 5–11 and 13 where 1.0 to 1.2 equiv of the diene was used. b) Anhydrous CH_3CN was the reaction solvent except for entries 2 and 4. Reactions were carried out at 80 °C except for entry 5. c) All were isolated yields. d) Diastereomeric ratios [*d.r.*] were assigned by using ^1H and/or ^{13}C NMR. e) Anhydrous $(CHCl)_2$ was the reaction solvent. f) Reaction was carried out at 0 °C.

Table 2. Reactions of Chiral Allenamides **2**−**5** with Acrolein and MVK

entry	allenamides[a]	conditions[b]	time	products	yield[c]	[*d.r.*][d]
1	 **2**	100 °C	48 h	 **26**	37 %	63 : 37
2	 **3**	100 °C	46	 **27**	43	66 : 34
3	**3**	100 °C	89	 **29**	38	80 : 20
4	 **4**	110 °C	48	 **30**	60	75 : 25
5	**4**	110 °C	44	 **31**	44	67 : 33
6	**4**	$ZnCl_2$[e] 80 °C	15	**31**	41	60 : 40
7	 **5**	120 °C	48	 **32**	53	67 : 33

a) 2.0 equiv of heterodienes were used. b) Anhydrous CH_3CN was used as the reaction solvent. c) All yields were isolated yields. d) Diastereomeric ratios [*d.r.*] were assigned by using ^1H and/or ^{13}C NMR. e)10 mol% of $ZnCl_2$ was added as a 1 *M* solution in ether.

However, at the same time **1** remains reactive in these cycloaddition reactions.

We then examined reactions using chiral allenamides **2**−**5** which contain oxazolidinone groups. Reactions of these allenamides with acrolein and/or MVK are summarized in Table 2. There are two significant features that are noteworthy from this study. First, chiral allenamides **2**−**5** are more thermally stable than **1** since the allenamide **1** did not survive temperatures above 100 °C. Thus, they are easier to handle experimentally than **1**. Allenamide **5** containing Sibi's auxiliary appears to be the most robust chiral allenamide, providing cycloadduct **32** in 53% yield after heating at 120 °C for 48 h [entry 7]. Second, these oxazolidinone-substituted chiral allenamides can tolerate Lewis acidic conditions as indicated by $ZnCl_2$-catalyzed reaction of **4** containing Evans' auxiliary with acrolein [entry 6]. Although these cycloaddition reactions of chiral allenamides **2**−**5** provided lower stereoselectivity as well as yields than those of **1**, and although we are currently improving these reactions using other conditions, it is more important to note that these chiral allenamdies should be useful for other organic transformations given their ability to withstand higher temperature and Lewis acidic conditions.

Given the stereochemical assignment and contrast in the stereochemical outcome between reactions of **1** and those of **2**−**5**, we obtained minimized structures of chiral allenamides **1** and **2** using the Spartan Program [AM1 Calculation]. As shown in Figure 2, the allene fragment is essentially coplanar with the imidazolidinone or oxazolidinone ring as indicated by dihedral angles for O═CNC═C. In addition, our calculations showed no significant difference in the rotational barriers of **1**−**5**.

These models suggest that the observed diastereoselectivity is likely due to a preferred addition of heterodienes from the bottom (less crowded) face of all allenamides leading to the major isomer with correct stereochemistry. The phenyl group in allenamide **1**, which contains an imidazolidinone moiety, appears to be the closest to the allene fragment, thereby providing the best steric presence and leading to the highest diastereoselectivity. The phenyl group in **2**, which contains an oxazolidinone moiety, actually tilts away from the allene moiety, thereby diminishing a significant amount

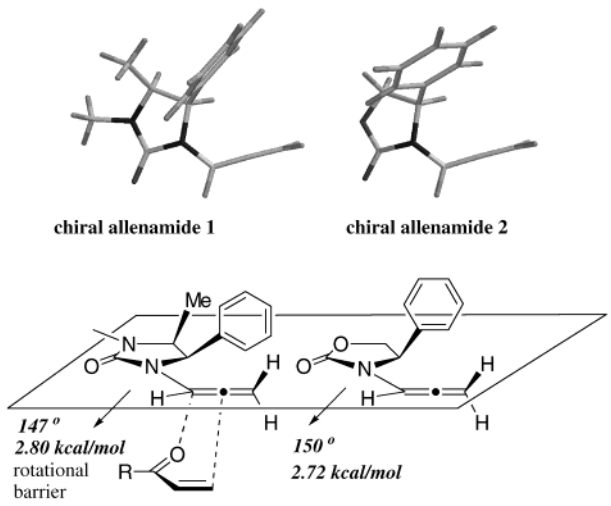


Figure 2. Minimized structures of chiral allenamides **1** and **2**.

of facial steric bias. The difference in stereoselectivity between chiral allenamides of **1** and **2**−**5** may also be attributed to the electronic difference between imidazolidinone and oxazolidinone. However, that is not as clear at this point and further mechanistic studies are being carried out.

Finally, we have attempted to demonstrate that these 2-arylpyranyl heterocycles **18**−**23** can be useful templates for further synthetic elaborations. Toward this purpose, we hydrogenated compound **23** and were able to obtain monohydrogenated and dihydrogenated products **33** and **34** in 50−80% yields [Figure 3]. The extent of hydrogenations may be controlled by using either Lindlar's catalyst or appropriate amounts of 5% Pd−C or Pt−C. More significantly, dihydropyran **33** was essentially obtained as a single isomer, while a diastereomeric ratio ranging from 87:13 to ≥96:4 was observed at the anomeric carbon of **34** [stereochemistry in **33** and **34** was assigned by NOE].

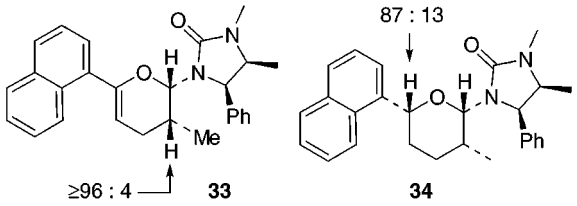


Figure 3.

We have described here the synthesis of a novel class of chiral allenamides and their stability as well as uncompromising reactivity as electron rich dienophiles in stereoselective inverse demand [4 + 2] cycloaddition reactions with heterodienes. We are currently exploring transformations involving these cycloadducts for preparations of unique *C*-aryl glycosides and natural products containing these pyranyl structural features. We are also investigating other synthetic methods using these chiral allenamides.

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Supporting Information Available: Experimental procedures and ^{1}H NMR spectral and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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