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The First Regioselective α-Deprotonation and Functionalization of Allenamides. An Application in Intramolecular Pauson–Khand-Type Cycloadditions

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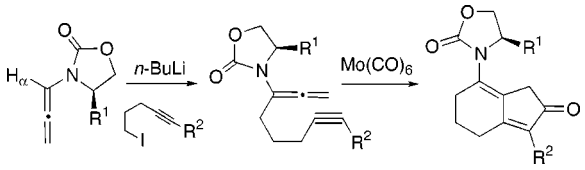
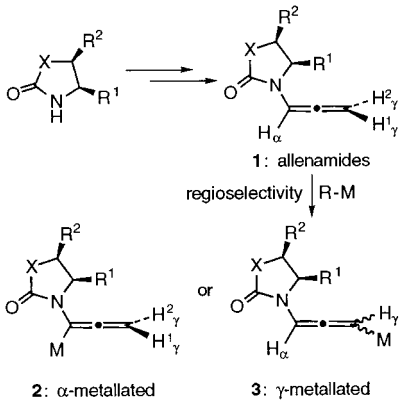
ABSTRACT



The first regioselective α-deprotonation and functionalization of electron-deficient allenamines are described here. The acidities of α- and γ-allenic protons of these allenamides are readily differentiated using strong bases, thereby allowing regioselective substitutions at either the α- or γ-allenic position. A specific synthetic application of the novel α-substituted allenamides in intramolecular Pauson–Khand-type cycloadditions is also described here.

We recently reported preparations and reactivities of a new class of nitrogen atom substituted allenes that demonstrate superior stability to the traditional allenamines.[2−4] The improved stability was a direct result of substituting an electron-withdrawing group on the nitrogen atom.[3,5] Our specific design for these allenamides features either an imidazolidinone or oxazolidinone moiety to provide access to chiral allenamides **1** [Scheme 1].[4] These chiral allenamides were shown to undergo inverse demand [4 + 2] cycloaddition reactions with heterodienes, leading to 2-arylpyranyl heterocycles with high diastereoselectivity.[4] Given the scarcity of synthetic applications involving allenamines[2] or electron-

Scheme 1



(1) UMN undergraduate research participant 1999−2000.

(2) 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.

(3) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, 6903.

(4) (a) Wei, L.-L.; Hsung, R. P.; Xiong, H.;Mulder, J. A.; Nkansah, N. T. *Org. Lett.* **1999**, *1*, 2145. (b) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. Submitted.

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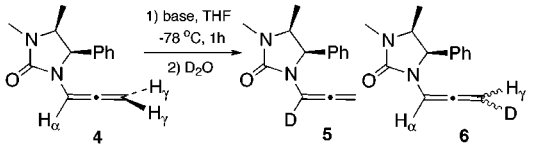
deficient allenamines,[6,7] we have continued our efforts in developing methodologies employing these allenamides as novel organic synthons. Specifically, we explored functionalizations at either the α- or γ-carbon of allenamides **1** via deprotonated allenamides **2** or **3**. Although regioselective deprotonations have been reported for allenamines[8] and allenol ethers,[2] deprotonations of allenamides and their subsequent reactivities have not been studied.[9] We report here our first success in regioselective deprotonations of allenamides and the applications of α-substituted allenamides in intramolecular Pauson−Khand-type cycloadditions.

The most important question to be addressed is whether the α- and γ-allenic protons in **1** possess sufficient difference in their acidities to allow regioselective deprotonations via appropriate bases. Toward this goal, we first examined deprotonations of the allenamide **4**. As summarized in Scheme 2, compound **4** was treated with a variety of bases

Scheme 2

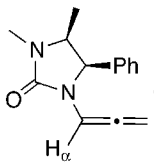
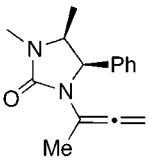
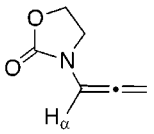
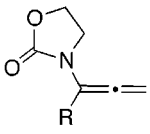
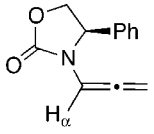
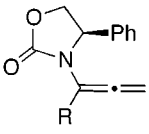
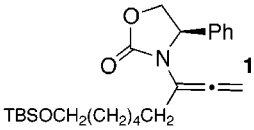
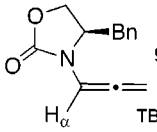
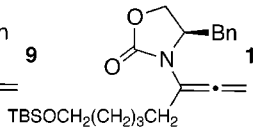
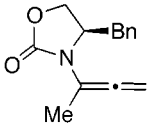


entry	base	eq	%D	yield of **4**+**5**+**6**	ratio of **5** : **6**
1	LHMDS	1.0	0 %	no reaction	--
2	LDA	1.0	50	not isolated	100 : 0
3	LDA	1.5	76	88 %	100 : 0
4	*n*-BuLi	1.0	50	not isolated	100 : 0
5	*n*-BuLi	1.5	75	88%	100 : 0
6	*n*-BuLi	2.0	100	90 %	100 : 0
7	*sec*-BuLi	1.5	70	not isolated	100 : 0
8	*t*-BuLi	1.0	67	76%	50 : 50

in various equivalents followed by quenching with D_2O. With the exception of LHMDS [entry 1], all of other bases surveyed were capable of deprotonating **4**. In most cases, the α-deuterated allenamide **5**[10] was observed as the only product, but when *t*-BuLi was used, the γ-deuterated allenamide **6** was also found in an equal amount [entry 7].[11a] The extent of deuteration[11b] at the α-carbon varied depending on the amount of base that was used. The use of *n*-BuLi [entries 4, 5, and 6] or LDA [entry 3] appears to be the most efficient, especially under the conditions shown in entry 6.

Having established the selectivity for α-deprotonation, we were able to efficiently functionalize the α-position of allenamides using various electrophiles. As summarized in Table 1, treatment of allenamines **4** and **7**−**9** using 1.2−1.5

Table 1

entry	starting allenamide[a]	product	yield[b]
1	 **4**	 **10**	90%
	 **7**		
2		**11**: R = Me	84
3		**12**: R = TMS	56
4		**13**: R = *n*-Bu_3Sn	92
	 **8**		
5		**14**: R = TMS	73
6		**15**: R = Bn	48
7[c]	**8**	 **16a**	58
8[c]	 **9**	 **16b**	25[d]
9	**9**	 **17**	85

a. All reactions were carried out in anhydrous THF and 1.25 eq of *n*-BuLi was used. b. Isolated yields. c. 1.1 eq of HMPA was used. d. 55% recovered starting material.

equiv of *n*-BuLi followed by additions of a variety of electrophiles such as silyl or stannyl chlorides and alkyl bromide or iodides provided the α-substituted allenamides **10**−**17** in 48−92% yields. The alkylation using a primary iodide such as $ICH_2[CH_2]_3CH_2OTBS$ or $ICH_2[CH_2]_4CH_2$-OTBS proceeded effectively, leading to **16a** and **16b** in 58% and 56% [based on recovered starting material] yields, respectively, when 1.0−1.2 equiv of HMPA was used [entries 7 and 8]. These second-generation allenamides are also quite stable, although **11** was found on occasions to undergo a rearrangement, giving rise to a 1,3-butadiene.

The most preferred conformation of these new allenamides is quite different from that of parent allenamides. For

(6) (a) Gardiner, M.; Grigg, R.; Sridharan, V.; Vicker, N. *Tetrahedron Lett.* **1998**, 435, and references cited therein. (b) Noguchi, M.; Okada, H.; Wantanabe, M.; Okuda, K.; Nakamura, O. *Tetrahedron* **1996**, *52*, 6581. (c) Farina, V.; Kant, J. *Tetrahedron Lett.* **1992**, 3559 and 3563.

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(8) (a) Tarasova, O. A.; Taherirastgar, F.; Verkruijsse, H. D.; Mal'kina, A. G.; Brandsma, L.; Trofimov, B. A. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 145. (b) Craig, J. C.; Ekwuribe, N. N. *Tetrahedron Lett.* **1980**, 2587.

(9) The only closest example would involve deprotonation of phosphoramide-substituted allenes: Corbel, B.; Paugam, J.-P.; Dreux, M.; Savignac, P. *Tetrahedron Lett.* **1976**, 835.

(10) All new compounds were identified and characterized by ^1H NMR, ^{13}C NMR, FTIR, $[\alpha]^{20}_D$, and MS.

(11) (a) The ratio of **5** to **6** was determined by D^2 NMR and GCMS. (b) The extent of deuteration at α-carbon was determined by ^1H NMR.

example, as shown in Figure 1, AM1 calculations reveal that the oxazolidinone rings or dipoles of the carbonyls groups are oriented in opposite directions in **8** and **18** [prepared from

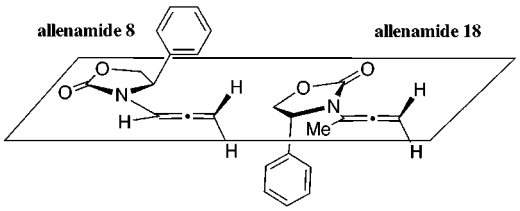
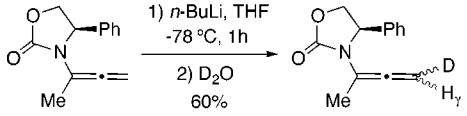


Figure 1.

methylating the α-lithiated allenamide **8**], although the oxazolidinone ring remains equally coplanar with the allenic moiety in both **8** and **18**. The conformational preference shown for **8** has been employed in the proposed mechanistic model for rationalizing the observed diastereoselectivity in [4 + 2] cycloaddition reactions of allenamides **4** and **7**−**9** with heterodienes.[4] We are currently examining the effect of the conformational preference of new chiral allenamides **10** and **14**−**18** on the stereochemical outcome of their reactions with heterodienes.

Having established the selectivity for the α-lithiation of allenamides, we further examined the potential of γ-lithiation. By blocking the α-position with a methyl group, deprotonation of the allenamide **18** at the γ-position using *n*-BuLi became feasible as shown in Scheme 3. Addition of D_2O to

Scheme 3



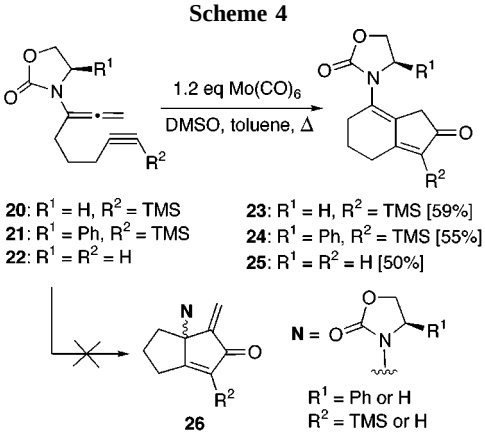
18 **19**: ratio: 2 : 1

γ-deprotonated **18** led to the γ-deuterated allenamide **19** in 60% yield. This result demonstrates that α- and γ-positions of the parent allenamides **4** and **7**−**9** can be functionalized in a sequential manner. In addition, we observed a modest but consistent diastereomeric induction in the γ-deprotonation.

To demonstrate the synthetic potential of α-metalated allenamides, the allenamides **20**−**21** were prepared in 57% and 70% yields, respectively, via alkylations of α-lithiated **7** or **8** using 5-iodo-1-trimethylsilyl-1-pentyne and 1.0−1.2 equiv of HMPA. The allenamide **22** was prepared in 70% yield via desilylation of **20** using K_2CO_3 in MeOH. A subsequent intramolecular Pauson−Khand-type reaction[12,13] of **20**−**22** using 1.2 equiv of $Mo(CO)_6$[14] provided the desired [2 + 2 + 1] cycloaddition products **23**, **24**, and **25** in 59%,

(12) (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (d) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (e) Brumond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283.

Scheme 4



26

55%, and 50% yields, respectively [Scheme 4]. To the best of our knowledge, these are the first examples of Pauson−Khand-type reactions involving nitrogen-substituted allenes.[15,16] These examples also suggest that our allenamides possess synthetic potential in transition metal mediated processes.

Although cycloadditions could take place at either the internal or terminal olefin, we only observed **23**−**25** resulting from participation of the terminal olefin in the cycloaddition, and did not find the other possible corresponding regioisomer [shown as **26**]. This regioselectivity is likely a result of the Mo metal complexing to the less sterically congested terminal olefin, thereby leading to the formation of bicyclic systems containing the enamide functionality which can be used for further synthetic transformation. This regioselectivity appears to agree with those reported by Brummond[15] for Pauson−Khand-type cycloadditions using 3,3-disubstituted allenes.

We have described here successful regioselective deprotonations of allenamides and demonstrated their subsequent synthetic potential in Pauson−Khand-type cycloadditions. We are currently developing a number of different intramolecular cycloaddition methodologies using new allenamides prepared from the deprotonation protocol described here.

Acknowledgment. R.P.H. thanks R. W. Johnson Pharmaceutical Research Institute for financial support.

Supporting Information Available: Experimental procedures as well as ^{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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(13) For some examples of cobalt-catalyzed Pauson−Khand reactions, see: (a) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285. (b) Belanger, D. B.; O'Mahony, D. J.; Livinghouse, T. *Tetrahedron Lett.* **1998**, 7637 and 7641. (c) Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159. (d) Lee, B. Y.; Chung, Y. K.; Jeong, N.; Lee, Y.; Hwang, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 8793.

(14) Jeong, N.; Lee, S. J.; Lee, B. Y.; Chung, K. Y. *Tetrahedron Lett.* **1993**, 4027.

(15) (a) Kent, J. L.; Wan, H.; Brummond, K. M. *Tetrahedron Lett.* **1995**, 2407. (b) Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535. (c) Brummond, K. M.; Wan, H. *Tetrahedron Lett.* **1998**, 931. (d) Ahmar, M.; Antras, F.; Cazes, B. *Tetrahedron Lett.* **1995**, 4417. (e) Ahmar, M.; Locatelli, C.; Colombier, D.; Cazes, B. *Tetrahedron Lett.* **1997**, 5281.

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