ORGANIC LETTERS

2001
Vol. 3, No. 23
3679−3681

Radical-Mediated Annulation Reactions. A Versatile Strategy for the Preparation of a Series of Carbocycles

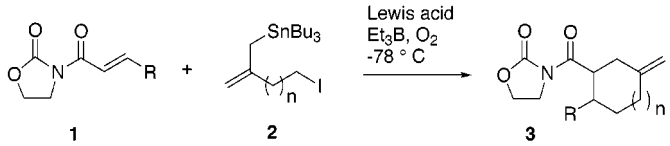
Mukund P. Sibi,* Jianxie Chen, and Tara R. Rheault

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58015

mukund.sibi@ndsu.nodak.edu

Received August 16, 2001

ABSTRACT



A series of novel 6-*endo* [4 + 2] and 7-*endo* [5 + 2] radical-mediated annulation reactions are described. These annulation sequences involve an intermolecular radical addition followed by intramolecular trapping with an allyltin moiety incorporated into the radical precursor fragment. This methodology allows for access to functionalized 6- and 7-membered carbocycles as well as bicyclic compounds with good to excellent levels of stereocontrol.

Free radical chemistry offers the advantage of multiple carbon−carbon bond formations in a single operation.[1] For instance, one can achieve this through an annulation sequence where two consecutive bond-forming reactions produce a cyclized product from simple precursors.[2] While cyclization reactions are abundant, examples of radical-mediated annulation reactions in which intermolecular bond formation is required are sparse in the literature and currently no general strategy is available that describes a stereoselective annulation methodology.[3] Limitations of the current status in the area of intermolecular addition−intramolecular cyclization include (1) the use of high temperature or photolysis initiation, (2) lack of a functional handle for stereocontrol on the radical precursor or acceptor, and finally (3) absence of the use of Lewis acid additives which are critical for diastereo- and enantioselective reactions.

Recently, we reported new methods for highly diastereoselective[4] and enantioselective[5] conjugate radical additions. Furthermore, we have described successful diastereoselective

(1) (a) For general aspects of tandem reactions, see the whole issue of *Chem. Rev.* **1996**, *96*, 6, issue 1. (b) Specifically see: Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) For radical reactions, see: Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (d) For information on cascade reactions, see: *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001.

(2) For early examples of radical-mediated annulation reactions, see: (a) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (b) Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 9401. (c) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. (d) Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, *48*, 2157. (e) Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, *48*, 2175. (f) Curran, D. P.; van Elberg, P. A. *Tetrahedron Lett.* **1989**, *30*, 2501. (g) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 941. (h) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 980. See also: (i) Srikrishna, A.; Hemamalini, P.; Sharma, G. V. R. *J. Org. Chem.* **1993**, *58*, 2509. (j) Maslak, V.; Cekovic, Z.; Saicic, R. N. *Synlett* **1998**, 1435. (k) Ward, D. E.; Gai, Y.; Kaller, B. F. *J. Org. Chem.* **1995**, *60*, 7830. (l) Feldman, K. S.;. Vong, A. K. K. *Tetrahedron Lett.* **1990**, *31*, 823. (m) Feldman, K. S.; Ruckle Jr., R. E.; Romanelli, A. L. *Tetrahedron Lett.* **1989**, *30*, 5845. (n) Feldman, K. S.; Berven, H. M. *Synlett* **1993**, 827. (o) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670. (p) Barton, D. H. R.; Zard, S. Z.; deSilva, E. *J. Chem. Soc., Chem. Commun.* **1988**, 285. (q) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135. (r) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2001**, *3*, 2709.

(3) For examples where relative stereochemistry is an issue in radical-mediated annulation reactions, see: (a) Brinza, I. M.; Fallis, A. G.; *J. Org. Chem.* **1996**, *61*, 3580. (b) Srikrishna, A.; Danieldoss, S. *J. Org. Chem.* **1997**, *62*, 7863. (c) Boiteau, L.; Boivin, J.; Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1998**, *37*, 1128. (d) Devin, P.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1998**, *63*, 6764. (e) Abazi, S.; Rapado, L. P.; Schenk, K.; Renaud, P. *Eur. J. Org. Chem.* **1999**, 477. (f) Evans, P. A.; Manangan, T. *J. Org. Chem.* **2000**, *65*, 4523. (g) Also see ref 2k.

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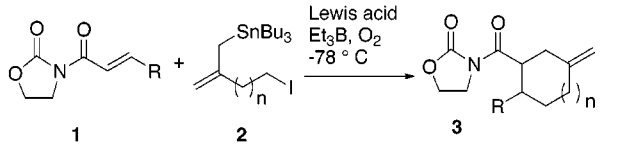
10.1021/ol016597k CCC: $20.00
Published on Web 10/17/2001

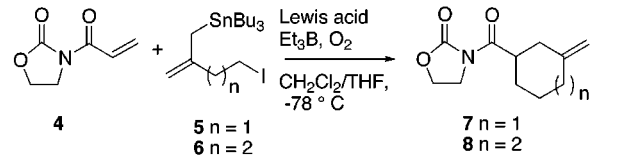
radical allylation sequences using functionalized (and simple) allylstannanes.[6] Having thus found ways to control absolute stereochemistry at both the α and β centers, it seemed a logical extension of this work to combine the radical precursor for β addition and the allylating agent into the same molecular fragment. The radical-mediated annulation sequence we envisioned is shown in Scheme 1. This arrangement should allow for intermolecular conjugate radical addition of precursor **2** to electron-deficient acceptor **1** followed by intramolecular trapping of the allylstannane functionality for a series of 6-*endo* [4 + 2] and 7-*endo* [5 + 2] annulation reactions. The scope and limitations of this methodology including control of relative and absolute stereochemistry are described herein.

Scheme 1



Initially we examined the formation of 6-membered rings using this methodology (Scheme 2).[7] Reactions with acrylate acceptor **4** and allyltin reagent **5** proceeded efficiently at −78 °C simply with Et_3B/O_2 initiation even in the absence of Lewis acid additives. This result is a function of the initial bond-forming step where the acrylate is a very good radical acceptor and Lewis acid activation is not essential for the conjugate radical addition. However, yields are improved with the addition of the appropriate Lewis acid. Moreover, compatibility with Lewis acids will allow for annulation sequences with less reactive acceptors and offers a means for stereocontrolled reactions. Results illustrating the effect of varying the Lewis acid are shown in Table 1. Several lanthanide (entries 2−5) and conventional Lewis acids (entries 6−9) were screened, and of these $Yb(OTf)_3$ offered the most efficient formation of the cyclized product **7** (entry 2). Slightly less efficient were the [5 + 2] annulations leading to 7-membered ring **8** (entries 10 and 11). Here reactions using $Yb(OTf)_3$ resulted in a yield of 61% for the desired 7-membered ring product (compare entries 2 and 10).

Scheme 2



(6) (a) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190. (b) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (c) Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122*, 8873.

(7) For experimental details, see Supporting Information.

Table 1. Effect of Lewis Acid on Radical Annulation

entry	Lewis acid[a]	allyltin reagent	product	yield (%)[b]
1	none	**5**	**7**	66
2	$Yb(OTf)_3$	**5**	**7**	77
3	$Y(OTf)_3$	**5**	**7**	67
4	$Sc(OTf)_3$	**5**	**7**	36
5	$Sm(OTf)_3$	**5**	**7**	71
6	$Zn(OTf)_2$	**5**	**7**	72
7	MgI_2	**5**	**7**	<10
8	$MgBr_2$	**5**	**7**	<10
9	$Mg(ClO_4)_2$	**5**	**7**	33
10	$Yb(OTf)_3$	**6**	**8**	61
11	$Zn(OTf)_2$	**6**	**8**	56

[a] 1 equiv of Lewis acid was used relative to the acceptor **4**. See Supporting Information. [b] Isolated yield.

Application of $Zn(OTf)_2$ offered similar yields for reactions with **6** (see entries 6 and 11).

Annulation reactions using either β-substituted acceptors **9** and **10** or substituted allyltin reagent **11** also allow for the efficient synthesis of carbocycles where relative stereochemistry between the newly formed stereocenters becomes an issue. This is shown in Table 2 (Scheme 3) where allyltin reagent **5** is added to crotonate **9**. Using $Sc(OTf)_3$ as a Lewis acid, the highest levels of diastereoselectivity were observed (20:1 *anti* selectivity, see entry 1). Moderate levels of selectivity (7:1) were also achieved using the slightly more reactive fumarate-derived substrate **10** and $Yb(OTf)_3$ as a Lewis acid (entry 3).

Scheme 3

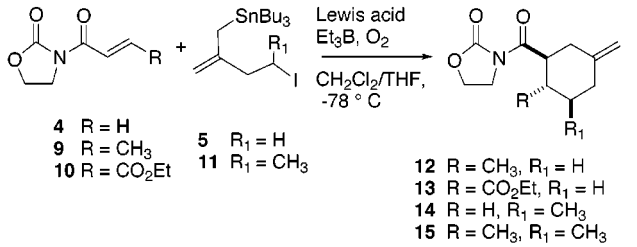


Table 2. Effect of Substituents on Radical Annulation

entry	R	R′	Lewis acid[a]	product	yield (%)	ratio[b]
1	CH_3	H	$Sc(OTf)_3$	**12**	63	20:1 (*anti*)
2	CH_3	H	$Yb(OTf)_3$	**12**	10[c]	
3	CO_2Et	H	$Yb(OTf)_3$	**13**	85	7:1 (*anti*)
4	H	CH_3	$Yb(OTf)_3$	**14**	68	7:1 (*syn*)
5	CH_3	CH_3	$Yb(OTf)_3$	**15**	85	1.5:1 (*anti*/ *anti*)

[a] 1 equiv of Lewis acid was used relative to the acceptors **4**, **9**, and **10**. See Supporting Information. [b] Diastereomer ratio determined by ^1H NMR (500 MHz). [c] Ethyl addition and allylstannane trapping product isolated in >30% yield.

Stereocontrol between substituents in the 1 and 3 positions on the 6-membered ring was also demonstrated. Selectivity favoring the *syn* product in a ratio of 7:1 was observed in the reaction of acrylate **4** with secondary iodide **11** (Table 2, entry 4). The observed relative stereochemistry can be rationalized by chair-like transition state models for 1,2 stereoinduction (Figure 1a) and 1,3 stereoinduction (Figure

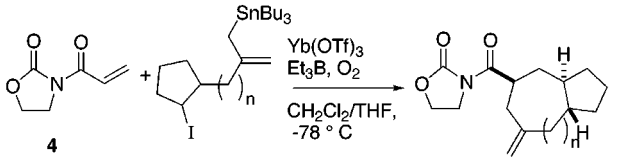
Figure 1.

1b) showing equatorial organization of substituents which is consistent with the Beckwith−Houk models.[2k,8]

The formation of three contiguous stereocenters has also been accomplished by following this strategy. Reaction of prochiral crotonate acceptor **9** and secondary iodide **11** provided product **15** as only two diastereomers in a 1.5:1 ratio and 85% yield (Table 2, entry 5). Extensive NOE studies identified the major product as shown in Scheme 3 and the minor product as the epimer at the 3-position. The low diastereoselectivity in this case is most likely due to the relative stereochemistry established during the initial diastereoselective radical addition step.[9]

By further functionalizing the allyltin unit, one can gain access to bicyclic compounds using this methodology. Scheme 4 describes the synthesis of 5,6 and 5,7-membered

Scheme 4



hydrindane and azulene systems **18** and **19**. Here also three stereocenters are established with varying degrees of stereocontrol. It is noteworthy to point out that the products obtained in these reactions contain convenient handles for further functionalization toward natural product targets. Figure 2 shows key NOE enhancements for determination

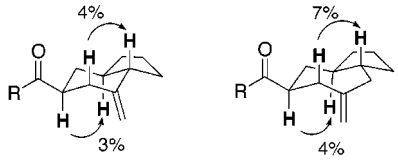
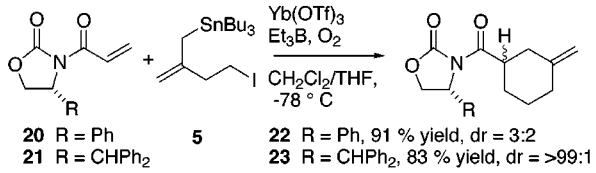


Figure 2.

of the major product for the 6,5- and 7,5-ring systems, respectively.

Excellent levels of absolute stereocontrol are also exhibited using this methodology and the appropriate choice of chiral auxiliary. Scheme 5 shows the application of two different

Scheme 5



chiral auxiliaries and their resultant effect on the diastereoselectivity of the annulation. The 4-diphenylmethyl oxazolidinone chiral auxiliary[10] developed by our group provided outstanding levels of selectivity (>99:1), demonstrating complete stereocontrol for the allylation (ring-closing) step.[11]

In conclusion, the methodology described in this work is an efficient, stereoselective radical-mediated annulation strategy for the formation of carbocycles. This methodology has the potential for the incorporation of functionality into the acceptor as well as the radical precursor/trap. Finally, it is notable that the bicyclic compounds prepared by following this route are known to be important core structures of many biologically interesting compounds. Future work includes developing enantioselective methodology using chiral Lewis acid catalysis.

Acknowledgment. This work was supported by a grant from the National Institute of Health (GM-54656). This material is also based upon work supported under a National Science Foundation Graduate Fellowship to Tara Rheault.

Supporting Information Available: Characterization data for compounds **5**−**22** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Sibi, M. P.; Rheault, T. R. Unpublished results.

(10) Sibi, M. P. *Aldrichimica Acta* **1999**, *32*, 93.

(11) We have not established the stereochemistry of the newly formed center. However, on the basis of our previous work we predict that allyl trapping should occur from a face opposite to the oxazolidinone 4-substituent resulting in the (*R*)-configuration.