

**Highly diastereoselective radical addition-cyclization strategy: facile synthesis of substituted furans.** Sibi, Mukund P.; Rheault, Tara R.; Miyabe, Hideto; Patil, Kalyani; Jasperse, Craig P.. **Comptes Rendus de l'Academie des Sciences, Serie IIC: Chimie** (2001), 4(7), 581-584.  
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**Radical-Mediated Annulation Reactions. A Versatile Strategy for the Preparation of a Series of Carbocycles**

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[\*\*] This work was supported by a grant from the National Institute of Health (GM-54656).

Free radical chemistry offers the advantage of multiple carbon-carbon bond formations in a single operation.<sup>[2]</sup> For instance, one can achieve this through an annulation sequence where two consecutive bond-forming reactions produce a cyclized product from simple precursors.<sup>[3]</sup> Examples of radical-mediated annulation reactions in the literature are sparse and currently no general strategy is available that describes a stereoselective annulation methodology.<sup>[4]</sup> Limitations of the current status in this area include (1) the use of high



2] and 7-endo [5 + 2] annulation reactions. The scope and limitations of this methodology including control of relative and absolute stereochemistry is described herein.

Initially we examined the formation of 6-membered rings using this methodology.<sup>[8]</sup> Reactions with acrylate acceptor **4** and allyltin reagent **5** proceeded efficiently at -78 °C simply with Et<sub>3</sub>B/O<sub>2</sub> 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)<sub>3</sub> offered the most efficient formation of the cyclized product **7** (entry 2). Slightly less efficient were the [5+2] cyclizations leading to 7-membered ring **8** (entries 10 and 11). Here reactions using Yb(OTf)<sub>3</sub> resulted in a yield of 61% for the desired 7-membered ring product

(compare entries 2 and 10). Application of  $\text{Zn}(\text{OTf})_2$  offered similar yields for reactions with **6** (see entries 6 and 11).

Annulation reactions using either  $\alpha$ -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 (equation 3) where allyltin reagent **5** is added to crotonate **9**. Using  $\text{Sc}(\text{OTf})_3$  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 a slightly more reactive fumarate-derived substrate **10** and  $\text{Yb}(\text{OTf})_3$  as a Lewis acid (entry 3).

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 1b) showing equatorial organization of substituents which is consistent with the Beckwith-Houk models.<sup>[9]</sup>

Figure 1a.

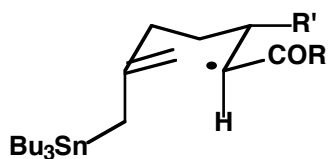
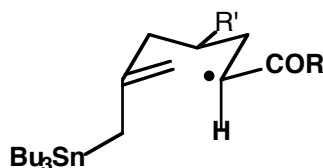


Figure 1b.



The formation of three contiguous stereocenters has also been accomplished 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 eqn (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 double-diastereoselective radical addition step.<sup>[10]</sup>

By further functionalizing the allyl tin unit one can gain access to bicyclic compounds using this methodology. Equation 4 describes the synthesis of 5,6 and 5,7-membered hydrindane and azulene systems **18** and **19** (eqn 4). Here also 3 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 towards natural product targets. Figures 2a and 2b show key NOE enhancements for determination of the major product for the 6,5- and 7,5- ring systems respectively.

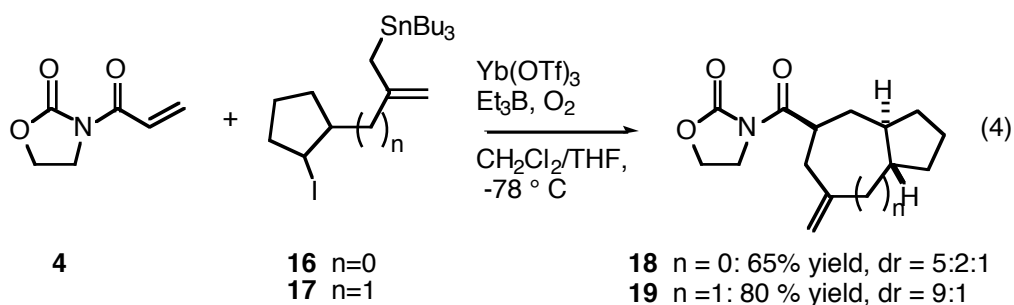
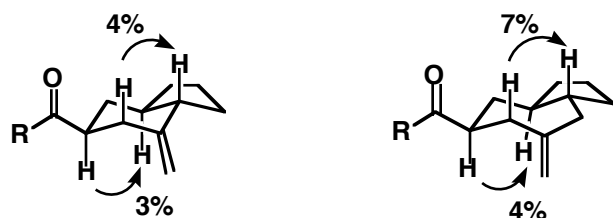
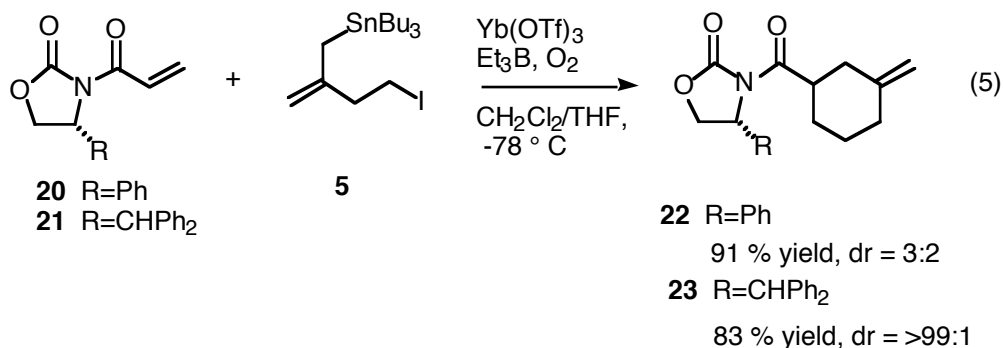


Figure 2a.

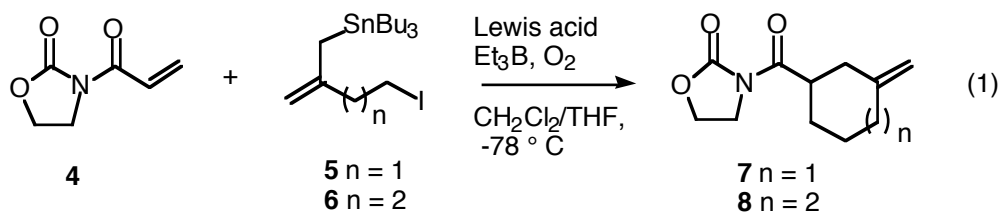
Figure 2b.



Excellent levels of absolute stereocontrol are also exhibited using this methodology and the appropriate choice of chiral auxiliary. Equation 5 shows the application of two different chiral auxiliaries and their resultant effect on the diastereoselectivity of the annulation. The 4-diphenylmethyl oxazolidinone chiral auxiliary<sup>[11]</sup> developed by our group provided outstanding levels of selectivity (>99:1) demonstrating complete stereocontrol for the allylation (ring-closing) step.

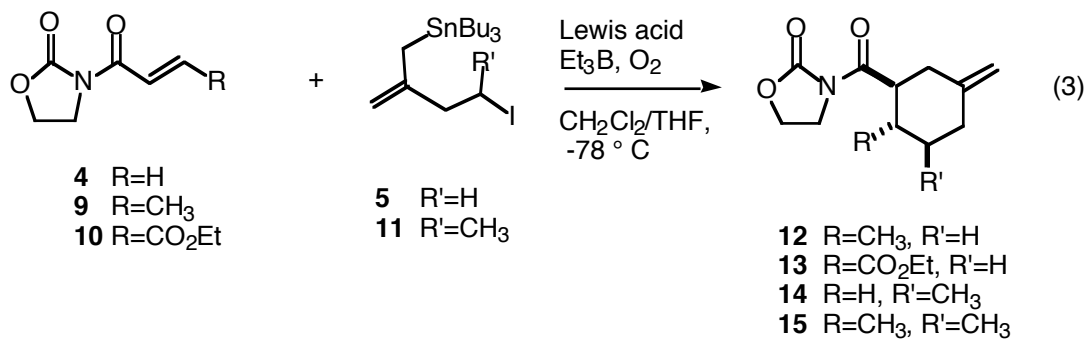


In conclusion, the methodology described is an efficient, stereoselective radical-mediated annulation strategy for the formation of complex carbocycles. We have also demonstrated that functionality can easily be incorporated into both the acceptor as well as the radical precursor/final trap. Finally, it is notable that the bicycles prepared 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.

**Table 1.** Effect of Lewis acid on Radical Annulation

Entry	Lewis acid <sup>a</sup>	Allyltin Reagent	Product	Yield (%) <sup>b</sup>
1	none	5	7	66
2	$\text{Yb}(\text{OTf})_3$	5	7	77
3	$\text{Y}(\text{OTf})_3$	5	7	67
4	$\text{Sc}(\text{OTf})_3$	5	7	36
5	$\text{Sm}(\text{OTf})_3$	5	7	71
6	$\text{Zn}(\text{OTf})_2$	5	7	72
7	$\text{MgI}_2$	5	7	<10
8	$\text{MgBr}_2$	5	7	<10
9	$\text{Mg}(\text{ClO}_4)_2$	5	7	33
10	$\text{Yb}(\text{OTf})_3$	6	8	61
11	$\text{Zn}(\text{OTf})_2$	6	8	56

<sup>a</sup> 1 Equiv. of Lewis acid was used. <sup>b</sup> Isolated yield.

**Table 2.** Effect of Substituents on Radical Annulation

Entry	R	R'	Lewis acid <sup>a</sup>	Product	Yield (%)	Ratio <sup>b</sup>
1	CH <sub>3</sub>	H	Sc(OTf) <sub>3</sub>	<b>12</b>	63	20:1(anti)
2	CH <sub>3</sub>	H	Yb(OTf) <sub>3</sub>	<b>12</b>	10 <sup>c</sup>	-
3	CO <sub>2</sub> Et	H	Yb(OTf) <sub>3</sub>	<b>13</b>	85	7:1(anti)
4	H	CH <sub>3</sub>	Yb(OTf) <sub>3</sub>	<b>14</b>	68	7:1(syn)
5	CH <sub>3</sub>	CH <sub>3</sub>	Yb(OTf) <sub>3</sub>	<b>15</b>	85	1.5:1(anti/anti)

<sup>a</sup> 1 Equiv. of Lewis acid was used. <sup>b</sup> Diastereomer ratio determined by <sup>1</sup>H NMR (500 MHz). <sup>c</sup> Ethyl addition and allylstannane trapping product isolated in >30% yield.

## References and Footnotes

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