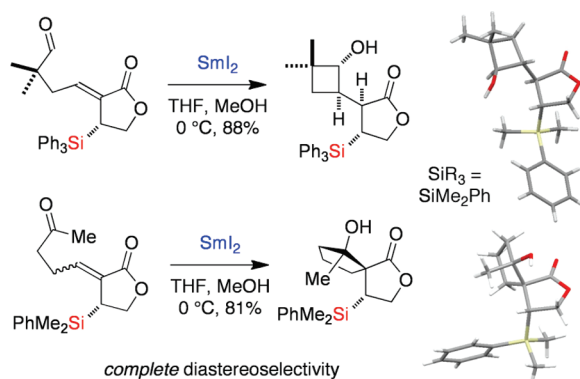


SmI<sub>2</sub>-Mediated Radical Cyclizations  
Directed by a C–Si BondHassan Y. Harb,<sup>†</sup> Karl D. Collins,<sup>†</sup> Jose V. Garcia Altur,<sup>†</sup> Sue Bowker,<sup>‡</sup>  
Leonie Campbell,<sup>‡</sup> and David J. Procter<sup>\*†</sup>*School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL,  
United Kingdom, and AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire,  
SK10 4TG, United Kingdom*

david.j.procter@manchester.ac.uk

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## ABSTRACT



The use of a silicon stereocontrol element in cyclobutanol and cyclopentanol-forming cyclizations mediated by SmI<sub>2</sub> results in excellent diastereocontrol. The C–Si bond in the products of cyclization provides a versatile handle for further manipulation. An asymmetric route to cyclization substrates involving copper-catalyzed silyl transfer has also been developed.

Since its introduction by Kagan,<sup>1</sup> samarium(II) iodide (SmI<sub>2</sub>) has become one of the most important reducing agents in organic synthesis.<sup>2</sup> The versatile reagent has been used to mediate many processes, ranging from functional group interconversions to complex carbon–carbon bond-forming

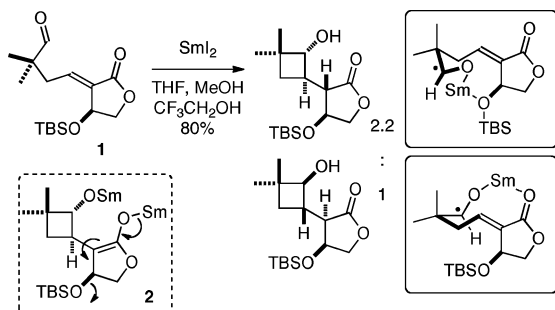
sequences.<sup>2</sup> Cyclization reactions are arguably the most useful transformations mediated by SmI<sub>2</sub>, and these have been used extensively in natural product synthesis.<sup>2b,d</sup>

We have developed a SmI<sub>2</sub>-mediated 4-*exo*-trig radical cyclization<sup>3</sup> to construct cyclobutanols and have employed the transformation in an approach to the pestalotiopsin and taedolidol natural products.<sup>4,5</sup> Unfortunately, attempts to

<sup>†</sup> University of Manchester.<sup>‡</sup> AstraZeneca.(1) (a) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5. (b) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.(2) For recent reviews on the use of samarium(II) iodide: (a) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis using Samarium Diodide: A Practical Guide*; RSC Publishing: Cambridge, 2010. (b) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140. (c) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607. (d) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (e) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. (f) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (g) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (h) Kagan, H.; Namy, J. L. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: Berlin, 1999; p 155. (i) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321.(3) (a) Weinges, K.; Schmidbauer, S. B.; Schick, H. *Chem. Ber.* **1994**, *127*, 1305. (b) Johnston, D.; McCusker, C. M.; Procter, D. J. *Tetrahedron Lett.* **1999**, *40*, 4913. (c) Johnston, D.; McCusker, C. F.; Muir, K.; Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 681. For discussions of other radical 4-*exo*-trig cyclizations, see: (d) Walton, J. C. *Top. Curr. Chem.* **2006**, *264*, 163. (e) Friedrich, J.; Walczak, K.; Dolg, M.; Piester, F.; Lauterbach, T.; Worgull, D.; Gansäuer, A. *J. Am. Chem. Soc.* **2008**, *130*, 1788.(4) (a) Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, *3*, 2001. (b) Johnston, D.; Couché, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2003**, *1*, 328. (c) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190. (d) Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5631.

control facial selectivity in the  $\text{SmI}_2$ -mediated 4-*exo*-trig radical cyclization using a silyl ether stereocontrol element, as in cyclization substrate **1**, resulted in low diastereocontrol (Scheme 1).<sup>4c</sup> Coordination to samarium(III) appears to com-

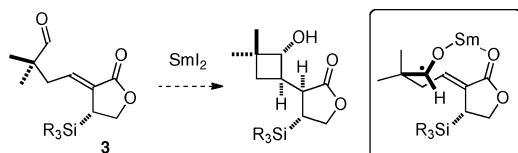
**Scheme 1.** Cyclization of a Silyl Ether Substrate



promise the role of the silyl ether as a “blocking” group. In addition, elimination of the silyloxy group from the intermediate  $\text{Sm(III)}$ -enolate **2** proved problematic (Scheme 1).<sup>4c</sup>

Here we describe a revised approach that exploits silicon connected to carbon as a stereocontrol element and in which cyclizations proceed with high to complete diastereocontrol. To our knowledge, this is the first example of a silicon substituent directing the stereochemical course of a cyclization reaction mediated by  $\text{SmI}_2$ .

**Scheme 2.** Proposed Cyclizations Directed by a C–Si Bond

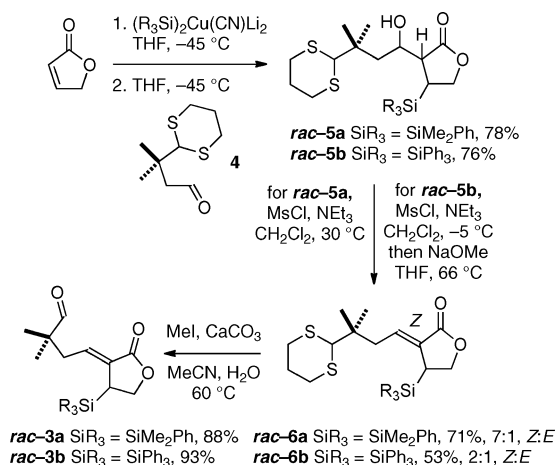


We proposed that attaching the silyl group directly to carbon in substrates **3** (cf. **1**) would remove the possibility of unwanted coordination to  $\text{Sm(III)}$  and elimination (see Scheme 1).

The silyl group would control the outcome of the reaction by blocking one face of the alkene, resulting in radical addition from the other. Furthermore, the synthetic equivalence of the C–Si bond to a C–O bond<sup>6</sup> would allow silicon-free cyclic products to be obtained and could minimize the use of hydroxyl protecting groups (Scheme 2).

The construction of the C–Si bond was used to facilitate the assembly of racemic cyclization substrates (Scheme 3). The one-pot conjugate addition of silyl cuprates<sup>7</sup> to (2*H*)-furanone

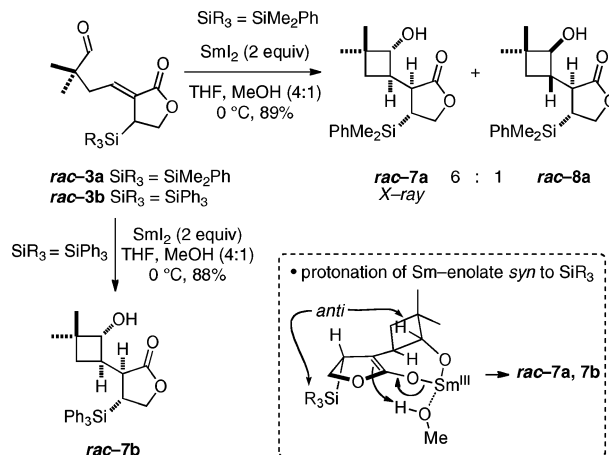
**Scheme 3.** Three-Step Synthesis of Cyclization Substrates



followed by quenching of the resultant enolate with aldehyde **4**<sup>3c</sup> gave aldol adducts **5** in good yield. Elimination of the mixed aldol diastereoisomers **5a,b** gave the required *Z*-alkenes **6a,b** as the major products (Scheme 3).<sup>8,9</sup> Removal of the thioacetal protection then gave the cyclization substrates **3a,b**. Thus, cyclization substrates **3** can be prepared in three steps from simple starting materials.

Pleasingly, treatment of **rac-3a** with  $\text{SmI}_2$  in THF–MeOH gave cyclobutanol **7a** as the major product in high yield with good diastereoselectivity (6:1 dr) (Scheme 4). Cyclization

**Scheme 4.**  $\text{SmI}_2$ -Mediated Cyclizations Directed by a Silyl Group



of **rac-3b** bearing a more bulky silyl group gave **7b** with complete diastereocontrol.<sup>10</sup> We were surprised to see that

(5) For other approaches to pestalotiopsin A, see: (a) Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, 8, 2429. (b) Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, 72, 7135. (c) Takao, K.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K. *Tetrahedron Lett.* **2005**, 46, 5815. (d) Takao, K.; Hayakawa, N.; Yamada, R.; Yamaguchi, T.; Morita, U.; Kawasaki, S.; Tadano, K. *Angew. Chem., Int. Ed.* **2008**, 47, 3426.

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(7) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527. (b) Ager, D. J.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1978**, 177. (c) Fleming, I.; Sarkar, A. K.; Doyle, M. J.; Raithby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2023.

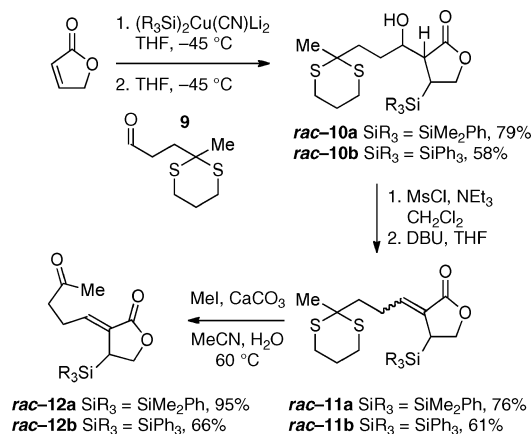
(8) The stereochemistry of the alkene isomers was assigned by comparison of NMR data with those of the closely related “OTBS” analogues. See ref 4c.

in all cases the intermediate Sm(III)-enolate<sup>11</sup> is protonated on the same face as the silicon group. This may arise from protonation by MeOH bound to the Sm(III) center (see Scheme 4). The relative stereochemistry in the cyclobutanol products was confirmed by NOESY experiments<sup>12</sup> and X-ray crystallographic analysis of **7a**.<sup>13</sup>

We have also assessed the value of a silicon stereocontrol element in SmI<sub>2</sub>-mediated reductive-aldol cyclizations developed in our group.<sup>14</sup>

The preparation of ketone cyclization substrates began with conjugate addition of silyl cuprates to (2*H*)-furanone followed by quenching of the resultant enolates with aldehyde **9**.<sup>15</sup> Adducts **10a,b** underwent elimination to give alkenes **11a,b** as inconsequential mixtures of isomers.<sup>16</sup> Finally, removal of the thioketal protection gave the cyclization substrates **12a,b** (Scheme 5).

**Scheme 5.** Four-Step Synthesis of Cyclization Substrates



Treatment of **rac-12a,b** with SmI<sub>2</sub> in THF-MeOH gave cyclopentanol **13a,b** with complete diastereocontrol (Scheme 6). The stereochemistry of **13a** and **13b** was confirmed by X-ray crystallographic analysis.<sup>13</sup>

The asymmetric synthesis of cyclization substrates is also possible.

(9) The alkene stereochemistry has a marked effect on the stereochemical outcome of the cyclizations of **3a**. See Supporting Information and also ref 4b.

(10) Surprisingly, the diphenylmethylsilyl analogue of **rac-3a** and **rac-3b** underwent cyclization to give products analogous to **rac-7a** and **rac-8a** in a 4:1 ratio, respectively (88% yield).

(11) For a review of the chemistry of samarium enolates, see: Rudkin, I. M.; Miller, L. C.; Procter, D. J. *Organomet. Chem.* **2008**, *34*, 19.

(12) See Supporting Information.

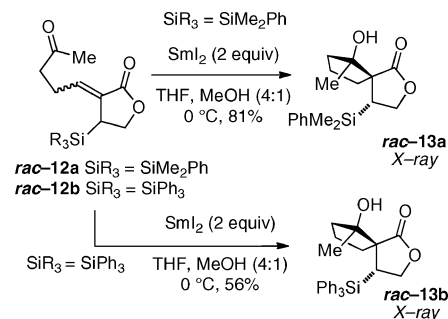
(13) See Supporting Information for X-ray structures and CCDC numbers.

(14) (a) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345. (b) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811. (c) Guazzelli, G.; Duffy, L. A.; Procter, D. J. *Org. Lett.* **2008**, *10*, 4291. (d) Sloan, L. A.; Baker, T. M.; Macdonald, S. J. F.; Procter, D. J. *Synlett* **2007**, 3155. (e) Baker, T. M.; Sloan, L. A.; Choudhury, L. H.; Murai, M.; Procter, D. J. *Tetrahedron: Asymmetry* **2010**, *21*, 1246.

(15) Wilken, J.; Winter, M.; Stahl, I.; Martens, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1067.

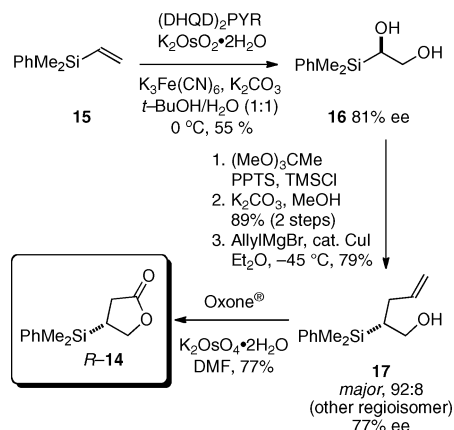
(16) The alkene stereochemistry has no effect on the stereochemical outcome of the cyclizations of **12a**. See Supporting Information and also ref 14b.

**Scheme 6.** Reductive-Aldol Cyclizations Directed by a Silyl Group



Silyl lactone **R-14** can be synthesized from vinylsilane **15** by Sharpless dihydroxylation<sup>17</sup> and conversion of the diol to unsaturated alcohol **17** (77% ee).<sup>18</sup> Oxidative cyclization of **17** then gave **R-14** (Scheme 7).<sup>19</sup>

**Scheme 7.** Asymmetric Approach to Cyclization Substrates



A more direct asymmetric approach to silyl lactone **R-14** utilizes Hoveyda's recently reported copper-catalyzed silyl transfer reaction.<sup>20</sup> Unfortunately, Hoveyda's optimal precatalyst system proved ineffective for silyl transfer to (2*H*)-furanone.<sup>21</sup> However, new precatalyst **18** was designed<sup>22</sup> and was found to give **R-14** in 67% yield and 82% ee (Scheme 8).

(17) (a) Kolb, C. H.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) For the Sharpless dihydroxylation of vinylsilanes, see: Vanhessche, K. P. M.; Sharpless, K. B. *Chem.—Eur. J.* **1997**, *3*, 517. Attempts to prepare silyl epoxides using Jacobsen's hydrolytic kinetic resolution were unsuccessful.

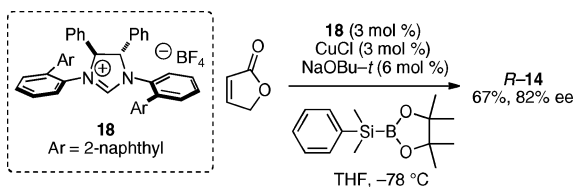
(18) (a) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515. (b) Bassindale, A. R.; Taylor, P. G.; Xu, Y. *Tetrahedron Lett.* **1996**, *37*, 555.

(19) Schomaker, J. M.; Travis, B. R.; Borhan, B. *Org. Lett.* **2003**, *5*, 3089.

(20) Lee, K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898.

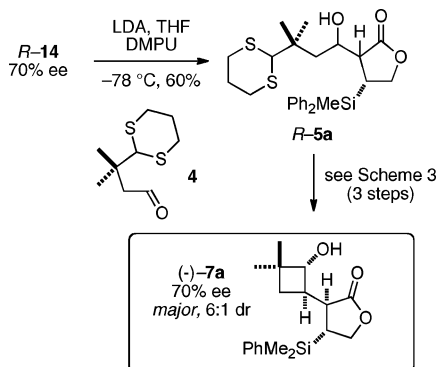
(21) For an alternative approach to asymmetric silyl transfer, see: (a) Walter, C.; Auer, G.; Oestreich, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5675. (b) Walter, C.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3818. (c) Walter, C.; Fröhlich, R.; Oestreich, M. *Tetrahedron* **2009**, *65*, 5513. (d) Hartmann, E.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6195.

**Scheme 8.** Improved Asymmetric Approach to Cyclization Substrates



Enantiomerically enriched *R*-**14** (70% ee) was then converted to *R*-**3a** using the sequence outlined in Scheme 3: aldol reaction with aldehyde **4**, elimination and deprotection gave *R*-**3a** in good overall yield. Subsequent treatment with  $\text{SmI}_2$  in THF-MeOH gave enantiomerically enriched cyclobutanol (–)-**7a** (70% ee, HPLC) (Scheme 9).

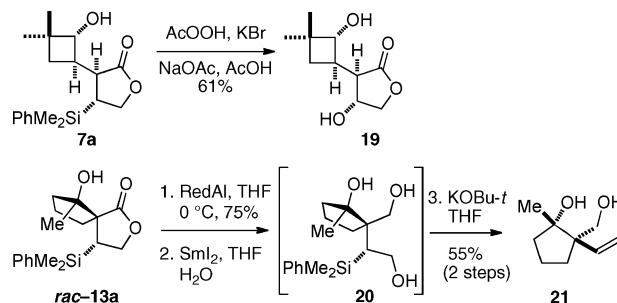
**Scheme 9.** Cyclization of an Enantiomerically Enriched Substrate



Finally, the C–Si bond in the products of directed cyclizations can be oxidized stereospecifically.<sup>6</sup> For example, oxidation of cyclobutanol **7a** under Fleming-Tamano conditions<sup>23</sup> gave diol **19** in moderate, unoptimized yield (Scheme 10). Alternatively,

(22) We found that C2-Symmetrical precatalysts with more sterically demanding substituents in the *ortho*-positions gave improved selectivity in additions to (2*H*)-furanone.

**Scheme 10.** Manipulation of the C–Si Bond in Cyclization Products



the C–Si bond can be used as a precursor to alkenes in a Peterson olefination.<sup>24</sup> Reduction<sup>25</sup> of **13a** gave triol **20** which underwent elimination under basic conditions to give **21** (Scheme 10).

In summary, we have shown the potential of a silicon group bonded directly to carbon as a stereocontrol element in  $\text{SmI}_2$ -mediated cyclizations during which two or three new stereocenters are formed. Preliminary studies show the value of the C–Si bond in cyclization products as a synthetic handle for further manipulation. A catalytic asymmetric route to cyclization substrates has been developed.

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**Supporting Information Available:** Additional experiments, full experimental details, characterization data and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds, chiral HPLC analyses, X-ray crystal structures for **7a**, **13a** and **13b**, CCDC numbers and cif files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(23) (a) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317. (b) Wendeborn, S.; Binot, G.; Nina, M.; Winkler, T. *Synlett* **2002**, 10, 1683.

(24) Ager, D. J. *Synthesis* **1984**, 5, 384.

(25) Attempts to convert **13a** directly to triol **20** with hydride reducing agents, including RedAl, led to decomposition. Partial reduction to the lactol and reduction with  $\text{SmI}_2\text{-H}_2\text{O}$  gave the best result. Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008**, 130, 1136.