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# $SmCp^R_2$-mediated cross-coupling of allyl and propargyl ethers with ketoesters and a telescoped approach to complex cycloheptanols†

Mateusz P. Plesniak, Xavier Just-Baringo, Fabrizio Ortu, David P. Mills* and David J. Procter*

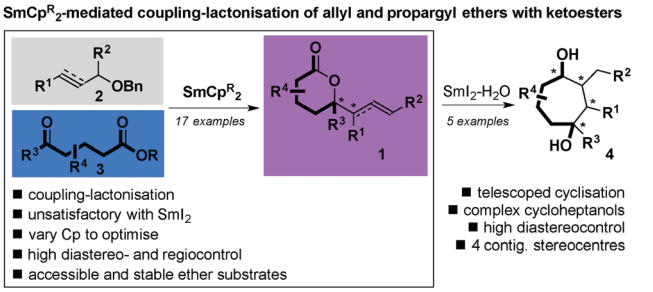
**A highly regio- and diastereoselective cross-coupling of allyl/propargyl ethers and δ-ketoesters, mediated by $SmCp^R_2$ reagents, delivers decorated δ-lactones. Screening of the Cp ligands on Sm(II) was employed to achieve high regio and diastereocontrol in some cases. Crucially, $SmI_2$ gave unsatisfactory results in the transformation. The process has been exploited in a telescoped approach to complex cycloheptanols in which two Sm(II) reagents act in turn on the simple starting materials.**

The latter half of the twentieth century saw the emergence of a new generation of metallic reductive ET reagents[1] for substrate activation.[2] At the vanguard of this new order was samarium(II) iodide ($SmI_2$, Kagan's reagent)[3] and since its first use in synthesis by Kagan,[4] it has become indispensable.[5] Unfortunately, some $SmI_2$-mediated processes proceed with unsatisfactory levels of stereo- and regiocontrol and the identification of alternative Sm(II) reagents that deliver improved results is desirable.[3–5]

δ-Lactones are important building blocks for synthesis and are motifs found in many bioactive targets.[6] Inspired by the seminal studies of Evans on the properties of $SmCp^*_2$[7] and of Kagan[8] and Takaki[9] on the allylation of simple, unfunctionalised ketones using $SmCp_2$ and $SmCp^*_2(THF)_2$, respectively, we envisaged a route to lactones **1** from allyl ethers **2** and δ-ketoesters **3** (Scheme 1). In stark contrast to $SmI_2$, $SmCp^R_2$ reagents have found limited use in preparative organic synthesis as ET reagents despite applications in organometallic synthesis and polymer science.[7–10] Crucially, $SmI_2$ proved to be unreactive towards allyl ethers and gave unsatisfactory results with allylic halides in the proposed coupling-lactonisation: δ-lactones were obtained with poor regio- and diastereocontrol.[11] Herein, we describe the optimisation of a $SmCp^R_2$-mediated approach to decorated δ-lactones **1** from allyl and propargyl ethers **2** and δ-ketoesters **3**.[12] To our knowledge, this is the first study examining the influence of substituents on the Cp ring on $SmCp^R_2$-mediated C–C bond-formation. Furthermore, we report a telescoped approach to complex cycloheptanols **4** (Scheme 1).

We began by preparing a family of $SmCp^R_2$ reagents **5a–f**, including novel complexes **5c**, **5e** and **5f**, with varying steric and electronic properties (Scheme 2). In line with Takaki's findings,[9] the high reducing ability of **5a,b,e,f** allowed readily prepared and stable allyl/propargyl ethers **2** to be used as substrates in the reductive cross-coupling ($SmI_2$–THF, *ca.* −1.8 V *vs.* SCE; $SmI_2$–$H_2O$, *ca.* −2.2 V *vs.* SCE; $SmCp^*_2(THF)_2$, −2.2 V *vs.* SCE).[13] We therefore used the coupling-lactonisation of **2a** and bifunctional ketone **3a** to evaluate the $Sm(II)Cp^R_2$ complexes with the aim of identifying a Sm(II) reagent capable of mediating a regio- and diastereoselective process. Notably, the use of $SmCp^R_2$ reagents allowed flexibility with regard to solvent choice – $SmI_2$ is almost exclusively used in THF – and toluene was found to provide optimal reactivity and selectivity in the coupling.

Pleasingly, Sm(II) reagents **5a,b** and **5e,f** gave the desired lactone isomer **1a** with high regiocontrol and with a preference for the formation of *anti*-**1a**, as confirmed by X-ray crystallographic




Scheme 1 A $SmCp^R_2$-mediated approach to decorated δ-lactones: reductive coupling of allyl/propargyl ethers and δ-ketoesters. A telescoped approach allows access to complex cycloheptanols.

*School of Chemistry, The University of Manchester, Oxford Rd, Manchester, M13 9PL, UK. E-mail: david.mills@manchester.ac.uk, david.j.procter@manchester.ac.uk*

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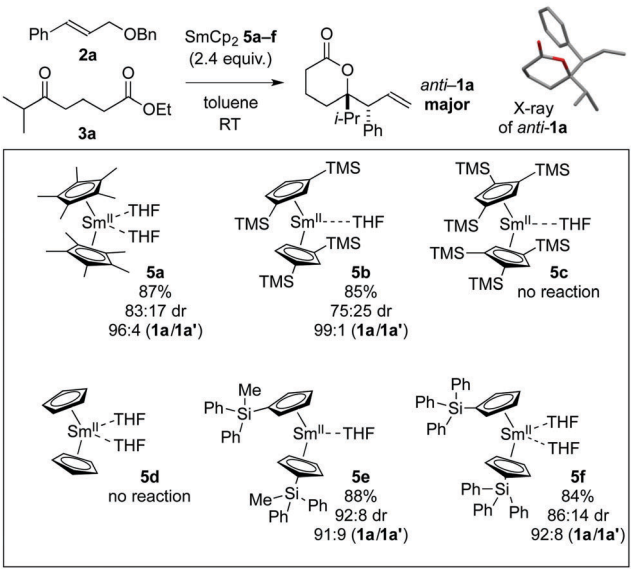
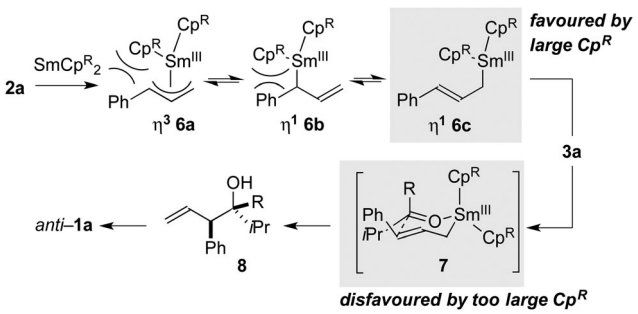



Scheme 2 Tailoring the $SmCp^{R}_{2}$ reagent for the regio- and diastereoselective coupling-lactonisation to give *anti*-**1a**. The minor regioisomer is **1a**′ (not shown).

analysis (Scheme 2).[14] A proposed mechanism for the coupling is shown in Scheme 3.[9]

To control the reactivity of allylic samarium(III) intermediate **6a**, we proposed that larger Cp ligands would favour reaction through $\eta^1$ organosamarium(III) **6c** *via* transition structure **7** to give the desired branched product **8**. However, if the Cp ligands were too large, the cyclic transition structure **7** may be disrupted and diastereocontrol lost. As the use of $SmCp^{*}_{2}(THF)_2$ **5a** gave *anti*-**1a** with moderate dr 83 : 17, we fine-tuned the steric characteristics of the $SmCp^{R}_{2}$ reagents by varying the nature and number of silylsubstituents on the Cp ligands. While bis-TMSCp ligands in **5b** (TMS – trimethylsilyl) gave excellent regiocontrol, lower diastereoselectivity was obtained in the coupling. Interestingly, tris-TMSCp complex **5c** and $SmCp_2$ **5d** proved unreactive. This is likely due to the steric hindrance associated with **5c** and the lower reducing ability of **5d**. Switching to the bulkier DPMSCp ligands in **5e** (DPMS = diphenylmethylsilyl) gave *anti*-**1a** with very good regiocontrol (91 : 9) and diastereocontrol (92 : 8 dr). Bulkier TPSCp ligands in **5f** gave *anti*-**1a** with lower diastereocontrol (TPS = triphenylsilyl). The ability to isolate




Scheme 3 Proposed mechanism and origin of regio- and diastereocontrol in the $SmCp^{R}_{2}$-mediated coupling of **2a** and **3a**. R = $(CH_2)_3CO_2Et$.

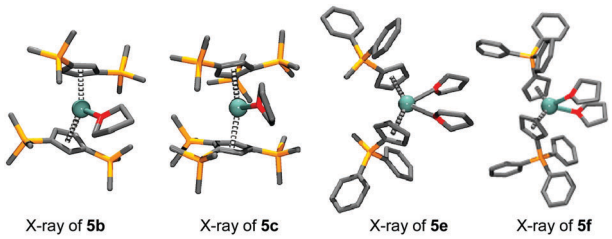


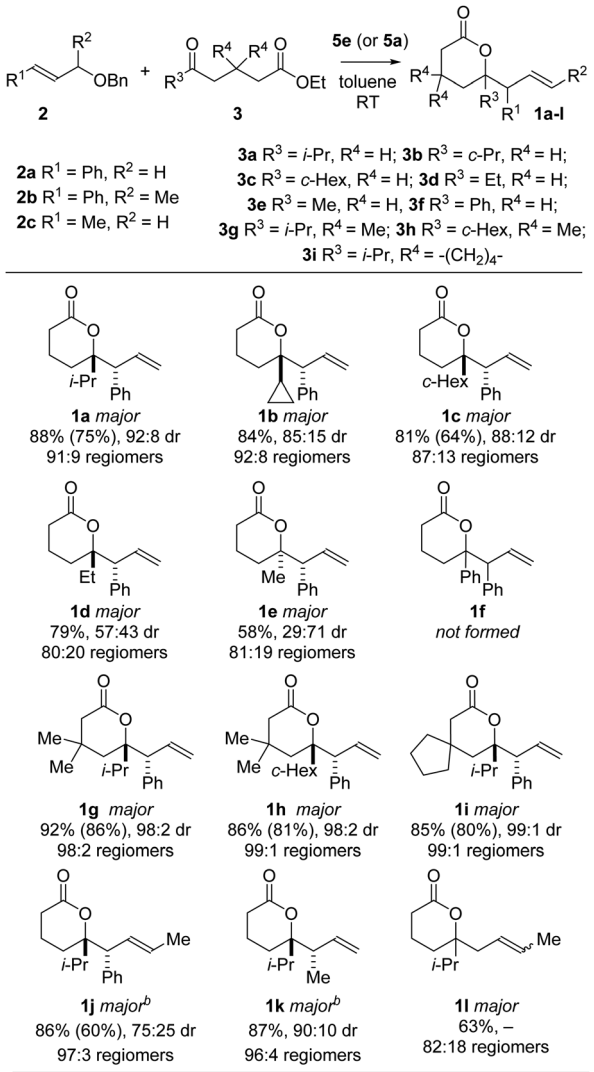

Fig. 1 X-ray characterisation of $SmCp^{R}_{2}$ reagents including novel complexes **5c**, **5e** and **5f**.

and characterise $SmCp^{R}_{2}$ reagents by X-ray crystallography, and thus understand the environment around the Sm(II) centre, is an advantage when tailoring their properties (Fig. 1). Complexes **5e** and **5f** are the first $SmCp^{R}_{2}$ systems bearing monosubstituted Cp ligands to be structurally characterised by X-ray crystallography.[14,15]

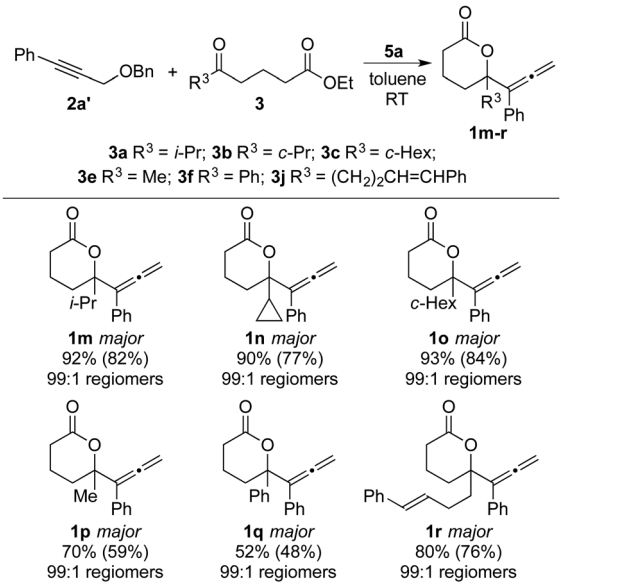
The scope of the $SmCp^{R}_{2}$-mediated coupling was explored using various allyl ethers **2** and ketoesters **3** (Scheme 4). Using $Sm(DPMSCp)_2(THF)$ **5e**, lactone adducts **1a–c** and **1g–i** were obtained with high diastereocontrol (up to 99 : 1) and high regiocontrol (up to 99 : 1) in good yield (81–92%). Little diastereocontrol was observed in the coupling of ethyl ketone **3d** to give **1d**. The reaction of methyl ketone **3e** resulted in a reversal of the observed diastereoselectivity and the formation of *syn*-**1e**, lending support to the six-membered transition state proposed for the reaction, in which the larger ketone substituent preferentially adopts an equatorial orientation (*cf.* Scheme 3). No lactone product was observed when analogous phenyl ketone **3f** was subjected to the cross-coupling procedure. Interestingly, the cross-coupling of (*E*)-((but-2-en-1-yloxy)methyl)benzene **2c** with **3a**, using **5e**, gave lactone **1l** as the major regioisomeric product. However, switching to the use of $SmCp^{*}_{2}THF_2$ **5a** allowed the opposite lactone regioisomer **1k** to be obtained from the same combination of coupling partners. Thus, fine-tuning of $SmCp^{R}_{2}$ reagents allowed partners to be united in complementary fashion. $SmCp^{*}_{2}(THF)_2$ **5a** was also found to be the optimal reagent for the cross-coupling of propargylic ether **2a**′ with keto esters **3** to give allenyl lactones **1m–r** in good to excellent yields (52–93%) and excellent regiocontrol in all cases (99 : 1) (Scheme 5).

Interestingly, the coupling of allyl/propargyl ethers **2** and ketoesters **3** can be telescoped with our previously reported lactone radical cyclisations using $SmI_2$–$H_2O$ to deliver decorated cycloheptanols **4**. The versatility, selectivity, and mutual compatibility of Sm(II) reagents[16] is key to the success of this telescoped ET approach that converts simple substrates to complex products. For example coupling of allyl ether **2a** and ketoesters **3a/c** using $SmCp^{R}_{2}$ reagent **5e**, followed by addition of $SmI_2$–$H_2O$ (5 fold excess to ensure complete conversion) and *in situ* ester–alkene radical cyclisation (*via* transition structure **I**),[17] gave the desired 7-membered carbocycles **4a** and **4b** which were isolated as single diastereoisomers in good overall yield (Scheme 6).[18] The intermediate δ-lactones **1a/c** are the most complicated substrates used to date in such radical cyclisations.[17,18] These radical cyclisations require ET to the ester carbonyl of complex δ-lactones **1** – a process made possible by the mixing of $SmI_2$ in THF with $H_2O$.[17] No cyclization was observed using $SmCp^{R}_{2}$.[11] Pleasingly, the analogous

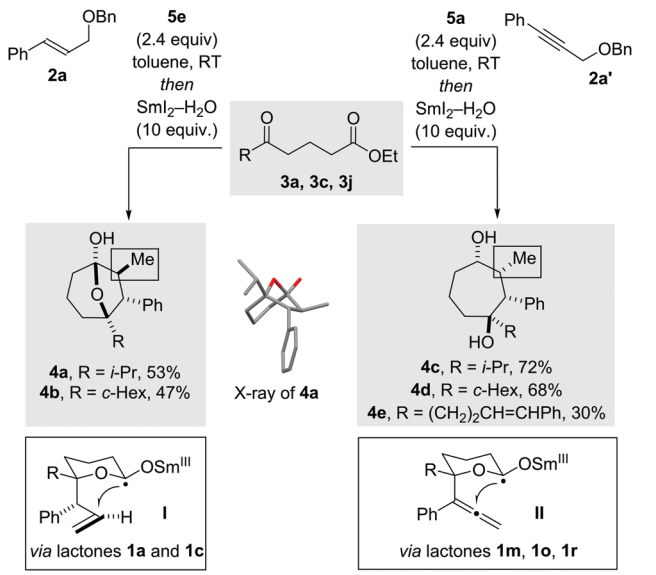
 




Scheme 4 Investigating the scope of the coupling mediated by Sm(II)$Cp^R_2$ reagents. [a] Diastereoselectivities, regioselectivities and yields (sum of diastereoisomers) were determined by $^1$H NMR using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard. Isolated yields in parentheses correspond to that of single regio- and diastereoisomers. [b] $Cp^*_2Sm(THF)_2$ **5a** was used.




Scheme 5 Investigating the scope of the coupling mediated by Sm(II)$Cp^R_2$ reagents. [a] Regioselectivities and yields were determined by $^1$H NMR using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard. Isolated yields in parentheses correspond to that of single regioisomers.




Scheme 6 A telescoped approach to complex cycloheptanols from simple starting materials using two Sm(II) reagents.

one pot process employing propargyl ether **2a′** and **3a/c/j** allowed both the chemo- and diastereoselectivity of the process to be switched: addition of $Cp^*_2Sm(THF)_2$ **5a** followed by $SmI_2$–$H_2O$ (1.7 fold excess) triggered cross-coupling and an ester–allene radical cyclisation (*via* transition structure **II**)[17,18] and resulted in the formation of cycloheptan-1,4-diol products **4c**, **4d** and **4e**, rather than hemiketal products, and with the opposite relative stereochemistry at the highlighted stereocentre.[19] Cycloheptanols **4c**, **4d** and **4e** were isolated as single diastereoisomers in good to high overall yield. The two complementary processes result in the formation of four contiguous stereocenters and two new carbon–carbon bonds in one pot.

In summary, we have optimised an approach to substituted δ-lactones that involves the regio- and diastereoselective coupling of allyl/propargyl ethers and ketoesters, mediated by $SmCp^R_2$ reagents. Screening of the Cp ligands on Sm(II) was employed to achieve high regio and diastereocontrol in some cases. Crucially, $SmI_2$ gave unsatisfactory results in the transformation. The process has been exploited in a telescoped approach to complex cycloheptanols in which two Sm(II) reagents act in turn on the simple starting materials.

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## Notes and references


1 C. Chatgilialoglu and A. Studer, *Encyclopedia of Radicals in Chemistry, Biology and Materials*, Wiley-Blackwell, Chichester, UK, 2012.

2 (*a*) A. Gansäuer and H. Bluhm, *Chem. Rev.*, 2000, **100**, 2771; (*b*) J. Streuff and A. Gansäuer, *Angew. Chem., Int. Ed.*, 2015, **54**, 14232; (*c*) W. J. Evans, *Inorg. Chem.*, 2007, **46**, 3435; (*d*) M. Szostak and D. J. Procter, *Angew. Chem., Int. Ed.*, 2012, **51**, 9238; (*e*) K. Takai, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, 2001; (*f*) A. Fürstner, *Chem. Rev.*, 1999, **99**, 991; (*g*) T. Hirao, *Chem. Rev.*, 1997, **97**, 2707; (*h*) Z. L. Shen, S. Y. Wang, Y. K. Chok, Y. H. Xu and T. P. Loh, *Chem. Rev.*, 2013, **113**, 271; (*i*) J. Justicia, L. A. de Cienfuegos, A. G. Campaña, D. Miguel, V. Jakoby, A. Gansäuer and J. M. Cuerva, *Chem. Soc. Rev.*, 2011, **40**, 3525.

3 D. J. Procter, R. A. Flowers and T. Skrydstrup, *Organic Synthesis Using Samarium Diiodide: A Practical Guide*, RSC Publishing, Cambridge, 2010.

4 (*a*) J. L. Namy, P. Girard and H. B. Kagan, *Nouv. J. Chim.*, 1977, **1**, 5; (*b*) P. Girard, J. L. Namy and H. B. Kagan, *J. Am. Chem. Soc.*, 1980, **102**, 2693.

5 (*a*) M. Szostak, N. J. Fazakerley, D. Parmar and D. J. Procter, *Chem. Rev.*, 2014, **114**, 5959; (*b*) K. C. Nicolaou, S. P. Ellery and J. S. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 7140; (*c*) M. Szostak, M. Spain, D. Parmar and D. J. Procter, *Chem. Commun.*, 2012, **48**, 330; (*d*) R. A. Flowers II, *Synlett*, 2008, 1427; (*e*) A. Dahlén and G. Hilmersson, *Eur. J. Inorg. Chem.*, 2004, 3393; (*f*) H. B. Kagan and J. L. Namy, Influence of solvents or additives on the organic chemistry mediated by diiodosamarium, in *Lanthanides: Chemistry and Use in Organic Synthesis*, ed. S. Kobayashi, Springer Berlin Heidelberg, Heidelberg, 1999, p. 155.

6 For selected, recent examples, see: (*a*) T. E. Smith, M. Djang, A. J. Velander, C. W. Downey, K. A. Carroll and S. van Alphen, *Org. Lett.*, 2004, **6**, 2317; (*b*) R. Doran, L. Duggan, S. Singh, C. D. Duffy and P. J. Guiry, *Eur. J. Org. Chem.*, 2011, 7097; V. Boucard, G. Broustal and J. M. Campagne, *Eur. J. Org. Chem.*, 2007, 225; (*c*) G. J. Florence, N. M. Gardner and I. Paterson, *Nat. Prod. Rep.*, 2008, **25**, 342; (*d*) A. Albrecht, Ł. Albrecht and T. Janecki, *Eur. J. Org. Chem.*, 2011, 2747; (*e*) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.*, 2011, **133**, 2714; (*f*) S. Bera, C. G. Daniliuc and A. Studer, *Org. Lett.*, 2015, **17**, 4940; (*g*) K. V. Chuang, C. Xu and S. E. Reisman, *Science*, 2016, **353**, 912.

7 (*a*) W. J. Evans, I. Bloom, W. E. Hunter and J. L. Atwood, *J. Am. Chem. Soc.*, 1981, **103**, 6507; (*b*) W. J. Evans, J. W. Grate, H. W. Choi, I. Bloom, W. E. Hunter and J. L. Atwood, *J. Am. Chem. Soc.*, 1985, **107**, 941; (*c*) W. J. Evans, J. W. Grate, L. A. Hughes, H. Zhang and J. L. Atwood, *J. Am. Chem. Soc.*, 1985, **107**, 3728; (*d*) W. J. Evans, L. A. Hughes, D. K. Drummond, H. Zhang and J. L. Atwood, *J. Am. Chem. Soc.*, 1986, **108**, 1722; (*e*) W. J. Evans and D. K. Drummond, *J. Am. Chem. Soc.*, 1986, **108**, 7440; (*f*) W. J. Evans and D. K. Drummond, *J. Am. Chem. Soc.*, 1989, **111**, 3329; (*g*) W. J. Evans, T. A. Ulibarri and J. W. Ziller, *J. Am. Chem. Soc.*, 1990, **112**, 219; (*h*) W. J. Evans, T. A. Ulibarri and J. W. Ziller, *J. Am. Chem. Soc.*, 1990, **112**, 2314; (*i*) W. J. Evans, T. A. Ulibarri and J. W. Ziller, *Organometallics*, 1991, **10**, 134; (*j*) W. J. Evans, R. A. Keyer and J. W. Ziller, *Organometallics*, 1993, **12**, 2618; (*k*) W. J. Evans, C. A. Seibel and J. W. Ziller, *Inorg. Chem.*, 1998, **37**, 770; (*l*) W. J. Evans, C. A. Seibel, J. W. Ziller and R. J. Doedens, *Organometallics*, 1998, **17**, 2103.

8 (*a*) J. Collin, J. L. Namy, C. Bied and H. B. Kagan, *Inorg. Chim. Acta*, 1987, **140**, 29; (*b*) J. L. Namy, J. Collin, J. Zhang and H. B. Kagan, *J. Organomet. Chem.*, 1987, **328**, 81; (*c*) C. Bied, J. Collin and H. B. Kagan, *Tetrahedron*, 1992, **48**, 3877; (*d*) J. Collin, J. L. Namy, F. Dallemer and H. B. Kagan, *J. Org. Chem.*, 1991, **56**, 3118; (*e*) H. B. Kagan, J. Collin, J. L. Namy, C. Bied, F. Dallemer and A. Lebrun, *J. Alloys Compd.*, 1993, **192**, 191.

9 (*a*) Y. Makioka, K. Koyama, T. Nishiyama, K. Takaki, Y. Taniguchi and Y. Fujiwara, *Tetrahedron Lett.*, 1995, **36**, 6283; (*b*) K. Takaki, M. Maruo and T. Kamata, *J. Org. Chem.*, 1996, **61**, 8332; (*c*) K. Takaki, T. Kusudo, S. Uebori, T. Nishiyama, T. Kamata, M. Yokoyama, K. Takehira, Y. Makioka and Y. Fujiwara, *J. Org. Chem.*, 1998, **63**, 4299.

10 (*a*) W. J. Evans, *J. Alloys Compd.*, 2009, **488**, 493; (*b*) W. J. Evans, *Coord. Chem. Rev.*, 2000, **206**, 263; (*c*) G. A. Molander and J. A. C. Romero, *Chem. Rev.*, 2002, **102**, 2161.

11 See ESI†.

12 Selected recent studies on the allylation of ketones: (*a*) T. Nakano, K. Endo and Y. Ukaji, *Chem. – Asian J.*, 2016, **11**, 713; (*b*) Y. C. Teo, J. D. Goh and T. P. Loh, *Org. Lett.*, 2005, **7**, 2743; (*c*) T. Takeda, M. Yamamoto, S. Yoshida and A. Tsubouchi, *Angew. Chem., Int. Ed.*, 2012, **51**, 7263; (*d*) J. Yadav, G. R. Stanton, X. Fan, J. R. Robinson, E. J. Schelter, P. J. Walsh and M. A. Pericas, *Chem. – Eur. J.*, 2014, **20**, 7122; (*e*) M. Raducan, R. Alam and K. J. Szabó, *Angew. Chem., Int. Ed.*, 2012, **51**, 13050; (*f*) R. Alam, T. Vollgraff, L. Eriksson and K. J. Szabó, *J. Am. Chem. Soc.*, 2015, **137**, 11262; (*g*) Y. Yamamoto and N. Asao, *Chem. Rev.*, 1993, **93**, 2207; Processes using $SmI_2$: (*h*) A. Krief and A. M. Laval, *Chem. Rev.*, 1999, **99**, 745.

13 (*a*) W. J. Evans, S. L. Gonzales and J. W. Ziller, *J. Am. Chem. Soc.*, 1994, **116**, 2600; (*b*) M. Szostak, M. Spain and D. J. Procter, *J. Org. Chem.*, 2014, **79**, 2522.

14 See ESI† for CCDC numbers.

15 For a $SmCp^R_3$ complex bearing monsubstituted Cp ligands, see: M. E. Fieser, M. R. MacDonald, B. T. Krull, J. E. Bates, J. W. Ziller, F. Furche and W. J. Evans, *J. Am. Chem. Soc.*, 2015, **137**, 369.

16 Alternative allylation procedures using transition metals are not compatible with a telescoped process. Transition metal salts lead to the decomposition of the $SmI_2$–$H_2O$ reagent essential for the second stage of the process. See ESI†.

17 X. Just-Baringo and D. J. Procter, *Acc. Chem. Res.*, 2015, **48**, 1263.

18 (*a*) I. Yalavac, S. E. Lyons, M. R. Webb and D. J. Procter, *Chem. Commun.*, 2014, **50**, 12863; (*b*) D. Parmar, H. Matsubara, K. Price, M. Spain and D. J. Procter, *J. Am. Chem. Soc.*, 2012, **134**, 12751; (*c*) K. D. Collins, J. M. Oliveira, G. Guazzelli, B. Sautier, S. De Grazia, H. Matsubara, M. Helliwell and D. J. Procter, *Chem. – Eur. J.*, 2010, **16**, 10240.


19 **4a** and **4b** are obtained as hemiketals as the α-methyl group on the top face hinders further reduction. In the formation of **4a,b** the stereochemistry at the highlighted position is established during the cyclisation event. In the formation of **4c,d,e** the stereochemistry at the highlighted position is established during conjugate reduction of a cycloheptenone intermediate, post cyclisation. Thus different relative stereochemical outcomes are observed. This is consistent with our previous findings. See ref. 18*b*.