Studies on the SmI_2-Promoted Pinacol-Type Cyclization: Synthesis of the Hexahydroazepine Ring of Balanol

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The efficiency of the samarium(II) iodide induced pinacol-type coupling for the construction of seven-membered cyclic amino alcohols has been investigated. With the acyclic carbonylhydrazones **6** and **16**, good yields of the hexahydroazepines **22** and **23** were obtained (56−57%) with high *trans*-selectivity (= 10:1), which compares well with similar reactions generating the corresponding five- and six-membered carbocycles (Fallis, A. G.; Sturino, C. F. *J. Am. Chem. Soc.* **1994**, *116*, 7447). It is essential for ring formation that the strongly electron-donating ligand, hexamethylphosphoramide, be present, as in its absense intermolecular pinacol coupling forming the diols **27**−**30** is the dominant reaction. Hence, the role for HMPA appears not only to increase the rate of electron transfer but also to modulate rate constants for the subsequent reactions (cyclization and pinacol coupling) of the intermediate ketyl. This ring forming reaction has been applied to the construction of the fully functionalized hexahydroazepine ring of the PKC inhibitor, balanol. Initial attempts to develop an asymmetric version of this reaction indicate the use of chiral ligands based on the structure of HMPA.

Introduction

The protein kinase C (PKC) inhibitor, balanol, has attracted much interest owing to its high inhibitory activity in the nanomolar range and novel structure, composed of a disubstituted hexahydroazepine ring and a highly functionalized benzophenone moiety (Figure 1).[1,2] The family of PKC enzymes has been associated with a variety of diseases, including cancer, cardiovascular disorders, asthma, diabetes, central nervous system dysfunction and AIDS.[3] The selective inhibition of these enzymes may therefore be of important therapeutic value, with balanol representing a new lead compound for achieving this goal. The synthetic community responded quickly to the challenge of preparing balanol and analogues thereof, with six total syntheses having been reported to date,[4] as well as several syntheses of key structural fragments.[5−7]

We have recently been interested in developing diastereoselective and enantioselective pinacol coupling

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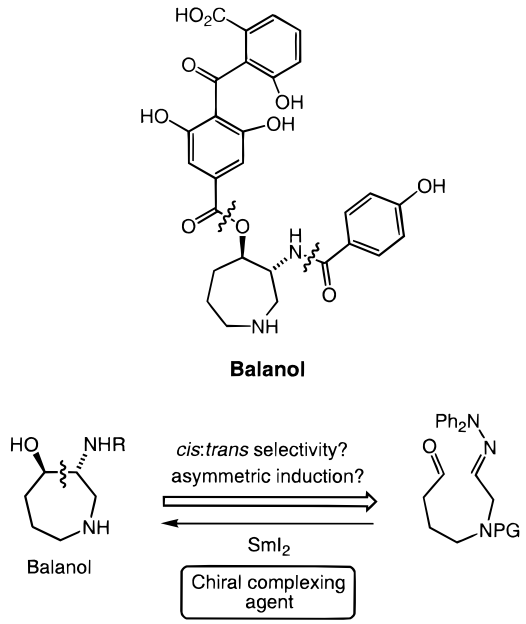
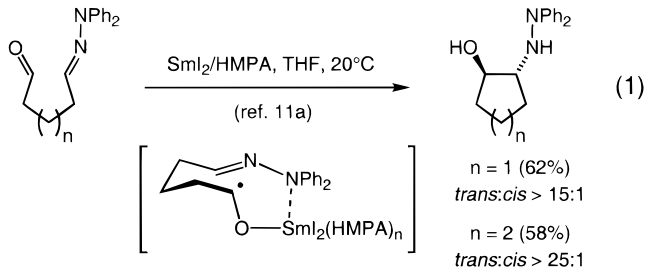


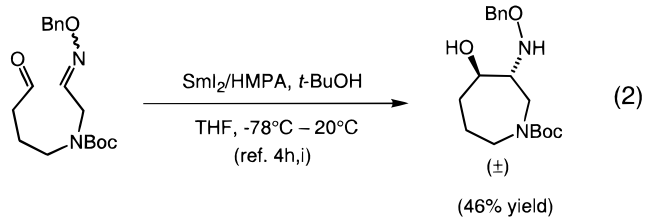
Figure 1.

reactions promoted by samarium diiodide.[8,9] A retrosynthetic analysis of balanol suggests that the hexahydroazepine ring, containing a vicinal amino alcohol with a *trans*-relationship, could possibly be constructed from an achiral precursor employing an enantioselective pinacol-type coupling between a monofunctionalized dialdehyde (Figure 1). Although SmI_2-promoted pinacol cyclizations of dialdehydes to five- and six-membered rings display an overwhelming desire for *cis*-diol formation involving a chelated intermediate,[10] the corresponding carbonylhydrazones have been reported by Fallis and Sturino to afford exclusively the *trans*-isomer (eq 1).[11,12] The observed selectivity was explained in the case of the cyclopentane formation by invoking a nine-membered ring template where the large diphenylhydrazone substituent occupies a pseudoequatorial orientation and the oxygen of the ketyl intermediate an axial position in order



(1)

to avoid arising gauche interactions in the product. For successful cyclizations of these room-temperature reactions, it was also noted that hexamethylphosphoramide (HMPA) was necessary as a cosolvent; in its absence, no reaction was observed under the same time scale. Whether this reaction could be adapted for seven-membered ring formation as required for the synthesis of the hexahydroazepine ring of balanol with the correct *trans*-selectivity was not obvious to predict, considering that a radical cyclization mechanism is invoked for seven-membered ring formation with cyclization rates possibly too slow to compete with the second electron transfer. In addition, an 11-membered chelate intermediate would be required for obtaining the correct relationship between the two stereogenic centers. Nevertheless, Naito and co-workers have recently applied this approach to the azapine ring of balanol employing a carbonyloxime derivative (eq 2)



(2)

and do indeed observe cyclization though with reduced diastereoselectivity (6.6 to 1 in favor of the *trans*-isomer).[4h,i,13,14] As with the diphenylhydrazones, the addition of HMPA was found indispensable, as in its absence no reaction was observed even at room temperature.

To develop an enantioselective version of this reaction, we initiated these cyclization studies with the diphenylhydrazones, being stereochemically defined compounds and not isomerical mixtures as with the corresponding oximes,[15] which is an important feature in both the design and rationalization of the SmI_2-promoted pinacol

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(12) For a recent review, see: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.

(13) In contrast to the diphenylhydrazones, which are stereochemically homogeneous compounds, the benzyloximes were prepared as a mixture of *cis*-and *trans*-isomers (2:3).

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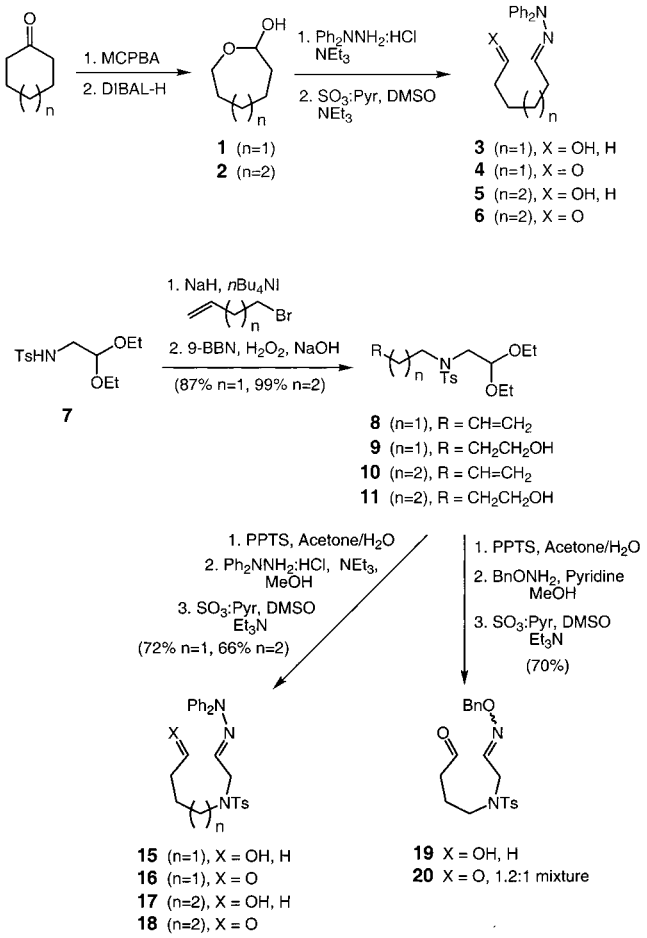
(15) In the total synthesis of balanol by Naito and co-workers,[4h,i] the enantiomerically pure hexahydroazepine fragment was obtained by optical resolution of the racemic product prepared after the ketyl cyclization step, followed by hydrogenolysis and acylation leading to the complete seven-membered ring unit.

Scheme 1

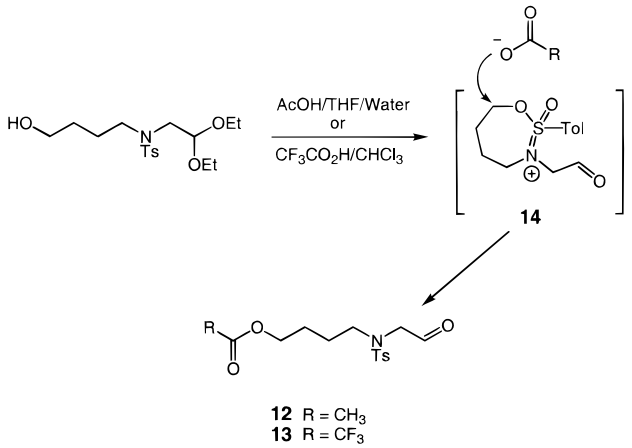


cyclization with asymmetric ligands. Hence, a clear picture of the mechanism of this reaction was required, including a more indepth comprehension of the role the presence of HMPA has for successful cyclizations. In this paper, we report that cyclization of carbonylhydrazones to seven-membered cyclic amino alcohols is also an efficient process affording the same high *trans*-selectivity as for the above smaller rings and provide evidence that HMPA not only serves to increase the reducing power of SmI_2,[16] but is *indispensable for promoting the pinacol cyclization itself*. We also suggest that HMPA is responsible for the *trans*-selectivity observed, without having to include a chelated ketyl intermediate.[11] Furthermore, initial studies for the development of an enantioselective pinacol cyclization induced by SmI_2 are presented.

Results and Discussions

Synthesis of the Cyclic Precursors. To study the cyclization reaction for the construction of balanol's disubstituted hexahydroazepine ring, a series of six-, seven- and eight-membered ring precursors were prepared according to Scheme 1. The carbonylhydrazones **4** and **6** were synthesized employing the protocol reported by Fallis and Sturino,[11a] involving initial Baeyer−Villiger oxidation of the corresponding cyclic ketone followed by DIBAL-H reduction, hydrazone formation and oxidation with DMSO and SO_3/Pyr.

Scheme 2



The preparation of the precursor to balanol's azepine ring was accomplished via a simple five-step synthesis (Scheme 1). Tosylamide **7** was *N*-alkylated with 4-butenyl bromide followed by conversion of the obtained alkene to its primary alcohol **9** by a hydroboration/oxidation sequence. However, subsequent hydrolysis of the acetal function to the corresponding aldehyde proved not to be such a facile task as exemplified when the acetal was subjected to standard hydrolysis conditions such as AcOH/THF/H_2O. Although the desired aldehyde was obtained in 60% yield, it was accompanied by a less polar aldehyde **12** (21% yield) in which the primary alcohol had been acetylated even in the presence of H_2O (Scheme 2). A similar result was observed under conditions such as $CF_3CO_2H/CHCl_3/H_2O$ furnishing the trifluoroacetate **13** in a 53% yield and only 14% of the desired aldehyde. The *N*-tosylamide function could be the possible culprit to this unwanted side reaction with the intervention of a seven-membered intermediate **14**, as shown in Scheme 2, from the acid-catalyzed expulsion of the hydroxyl group by the *N*-tosylamide.[17] Acetate attack and opening would then lead to either **12** or **13**.

Whereas the use of PTSA in THF/water leads to some decomposition, quantitative yields of the correct aldehyde were obtained by refluxing a 5% aqueous acetone solution of the diethyl acetal with 0.5 equiv of PPTS for 4 days. Subsequent hydrazone formation to **15** and oxidation afforded the carbonylhydrazone **16** as a crystalline solid (mp 94−96 °C) with an overall yield of 52% for the five steps.

The corresponding eight-membered ring precursor, the carbonylhydrazone **18**, and the benzyl oxime **20** were prepared under identical conditions as shown in Scheme 1 in high yields. The latter compound was obtained as a 1:1.2 mixture of *cis*- and *trans*-isomers at the carbon−nitrogen double bond.

Cyclization Studies. The conditions reported by Fallis and Sturino[11a] for promoting ring formation (SmI_2/HMPA) were first attempted with precursors **4** and **6**. Addition of a 0.1 M THF solution of SmI_2 (4 equiv) to a THF solution of **4** and HMPA (8−12 equiv) led to rapid consumption of the carbonylhydrazone affording essen-

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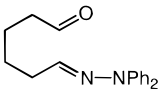
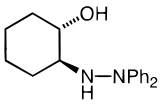
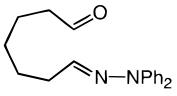
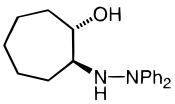
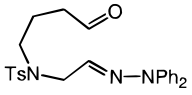
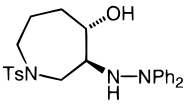
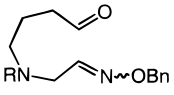
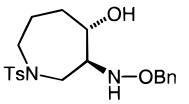
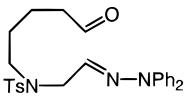
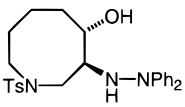
(17) Denieul, M.-P.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5495.

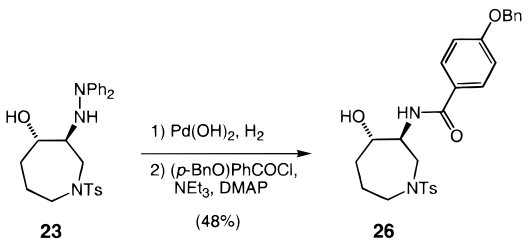
Table 1. Cyclization of Aldehydes 4, 6, 16, and 20 with SmI_2/HMPA

Entry	Acyclic precursor	Product (Yield)
1	 **4**	 **21** (57%) *trans*:*cis* > 15:1
2	 **6**	 **22** (57%) *trans*:*cis* > 15:1
3	 **16**	 **23** (59%) *trans*:*cis* = 10:1
4	 **20** (R = Ts)	 **24** (40%) *trans*:*cis* = 5:1
5	 **18**	 **25** (0%)

tially only one cyclic product **21** with the *trans*-stereochemistry in 57% yield, identical to that earlier reported (Table 1, entry 1). Repetition of this experiment with the homologue **6** proved equally rewarding, furnishing the disubstituted cycloheptane **22** in the same yield and high *trans*-selectivity (entry 2), the stereochemical proof of which will be described below. Somewhat surprising is the similarity of these two reactions in both yields and stereoselectivity, considering the anticipated greater rate constant for 6-*exo* cyclization in comparison to the 7-*exo* ring formation, and that the latter cyclization would require an 11-membered cyclic chelate compared to an equally unfavored 10-membered intermediate.[11a] In any event, this sole example suggests that the SmI_2-promoted pinacol cyclization of carbonylhydrazones also provides an efficient entry to seven-membered carbocycles.

When the same reaction conditions were applied to the acyclic derivative **16** (Table 1, entry 3), we were pleased to observe the formation of the desired hexahydroazepine ring **23** in 59% yield though with a slightly reduced *trans*:*cis* ratio of 10:1. The ^{1}H NMR shifts and coupling constants of the methine protons in the ring correspond well with those for similar compounds possessing the same *trans*-relationship between the vicinal substituents,[4] whereas with the isomeric *cis*-compound, the H4 proton is downfield shifted by 0.5 ppm to δ 4.05 compared to δ 3.52 for **23**. This assignment was based on 2D NMR techniques. This same trend was also observed with the *cis*- and *trans*-isomers of **21**, where the same protons are observed at 4.02 and 3.68, respectively. In the case of the cycloheptane derivative **22**, a ^{1}H NMR spectrum was noted similar to that of the *trans*-**21** where the CHO- and

Scheme 3



CHN- protons are observed at approximately 3.6 and 2.8 ppm, respectively, in addition to possessing similar coupling patterns. These observations also suggest that **22** possesses the same *trans*-relationship between the vicinal substituents.

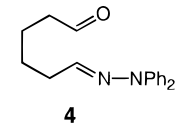
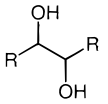
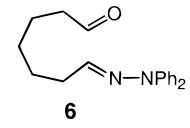
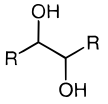
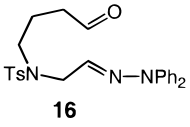
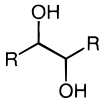
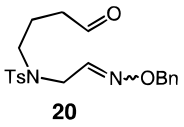
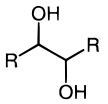
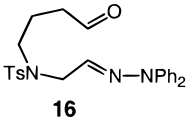
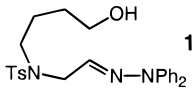
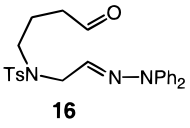
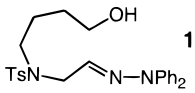
Attempts to cyclize the carbonyloxime **20** (R = Ts), an analogue of the Naito compound (R = BOC),[4h,i] resulted in a less clean reaction, and at best we could isolate the azepine ring in only a 40% yield with a *trans*:*cis*-ratio of approximately 5:1 (Table 1, entry 4). On the other hand, extension of this reaction to the creation of the eight-membered heterocyclic ring **25** from carbonylhydrazone **18** (entry 5) proved less rewarding with an array of compounds formed according to TLC analysis. Apparently, the limit in successful radical cyclizations has been reached with this attempted 8-*exo* ring closure event.

Definite confirmation for the *trans*-stereochemistry observed in the seven-membered ring closures was obtained by carrying **23** through to the complete structure of balanol's hexahydroazepine ring. Hence, a two-step procedure involving reduction of the hydrazine with Pearlman's catalyst/H_2[18] and acylation with *p*-benzyloxybenzoyl chloride (Scheme 3) afforded the corresponding crystalline *p*-benzyloxybenzamide **26** (mp 166−167 °C), of which its single crystal X-ray structure clearly reveals the *trans*-relationship between the two vicinal ring substituents (see Supporting Information).

To identify other conditions for improving both the cyclization yields and the *trans*:*cis*-selectivity, we next investigated the same intramolecular pinacol reactions employing SmI_2 alone. This was founded under the assumption that if a cyclic chelate indeed is the true intermediate in these ketyl-hydrazone additions, an increase in the *trans*-selectivity would be expected owing to the better Lewis acid properties of the metal ion in the absence of the electron-donating ligand, HMPA. However, the groups of Fallis and Naito report no reactivity without HMPA. This is somewhat puzzling considering that alkyl aldehydes have previously been known to undergo either intra- or intermolecular SmI_2-induced pinacol coupling in the absense of HMPA. More puzzling was it, when carbonylhydrazone **16** was subjected to SmI_2 in THF at room temperature, that consumption of the divalent lanthanide reagent was completed after only 10 min! However, the major compound isolated after workup was surprisingly not the cyclic product, of which none was detected, but the diol **29** (69%, approximately 1:1 mixture of diastereomers) from intermolecular pinacol coupling (Table 2, entry 3). This chemical divergence was unanticipated under the simple presumption that radical cyclizations should be favored

(18) Miyata, O.; Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 271.

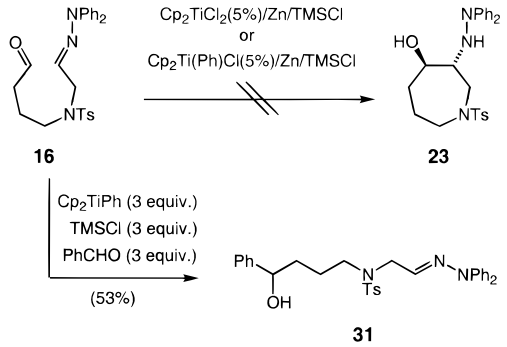
Table 2. Intermolecular Pinacol Coupling of Aldehydes 4, 6, 16, and 20 with SmI_2

Entry	Acyclic precursor	Product (Yield)
1	 **4**	 **27** (39%)
2	 **6**	 **28** (56%)
3	 **16**	 **29** (69%)
4	 **20**	 **30** (50%)
5[a]	 **16**	 **15**
6[b]	 **16**	 **15** + **23**

[a] Reaction was performed with $SmBr_2$ by pretreating the THF solution of SmI_2 with LiBr (10 equiv). See ref 21. [b] Reaction was performed as in entry 5 but with LiCl.

under these less reducing conditions.[19,20] The same tendency was observed with the carbonylhydrazones **4** and **6** (entries 1 and 2), as well as with the corresponding benzyloxime **20** (entry 4). Whereas **6** and **20** led to the formation of the vicinal diols **28** and **30** in 56% and 50% yield, respectively, the treatment of the six-membered ring precursor **4** with SmI_2 was less clean, affording several compounds. The major product was again identified as the diol **27** (39%) from intermolecular pinacol coupling. However, in this case the cyclic amino alcohol **21** could be isolated, albeit in a low yield (10%) and a low selectivity (*trans*:*cis*, 4:1). The other minor products were identified as esters arising from Tischenko side reactions.

Scheme 4



Attempts to promote the cyclization with in situ generated $SmBr_2$ and $SmCl_2$ were also made. Previous electrochemical investigations show that these reagents, prepared from SmI_2 with the corresponding lithium halide, are more potent reducing agents with oxidation peaks (−1.78 V for $SmBr_2$, −1.99 V for $SmCl_2$ vs Fc^+/Fc in THF)[21] similar or in the vicinity of SmI_2 complexed with four HMPA (−1.82 V) as determined by cyclic voltammetry.[20] It was therefore interesting to examine the effect that would be exerted on the cyclization event upon decreasing the oxidation potential of SmI_2 in the absence of the bulky hexamethylphosphoramide ligand. As shown in Table 2 (entries 5 and 6), treatment of the aldehyde **16** with SmI_2, previously subjected to either excess LiBr or LiCl, led either exclusively to the reduction of the aldehyde function to the corresponding primary alcohol as in **15** or to a 3:1 mixture of **15** and the cyclized product **21**, respectively, though in both cases without any traces of the diol **29**.

Finally, the recent findings that the low-valent titanium complexes, Cp_2TiCl[22] and the more reactive Cp_2TiPh,[23] catalyze the inter- and intramolecular pinacol couplings of alkyl aldehydes prompted us to investigate these reagents as possible candidates for promoting the cyclic amino alcohol formation. However, the catalytic procedures reported employing Cp_2TiCl_2(5%)/Zn/TMSCl or $Cp_2Ti(Ph)Cl$(5%)/Zn/TMSCl were ineffective in catalyzing the ring closure of carbonylhydrazone **16**. In one try, **16** was treated with both 3 equiv of Cp_2TiPh (prepared from Cp_2TiCl_2 with *i*PrMgCl and then PhMgBr) and TMSCl, but even after 24 h no sign of any reaction was observed. To test if Cp_2TiPh had indeed been generated in this reaction mixture, 1 equiv of benzaldehyde was added, resulting in the rapid consumption of aldehyde **16**. The major product isolated was the alcohol **31** (53% yield), in which phenyl group transfer had occurred from the titanium metal center to aldehyde **16** (Scheme 4). This reaction is most likely promoted by the corresponding Ti^{IV} pinacolate generated by the reaction of Cp_2TiPh with benzaldehyde or $Cp_2Ti(Ph)Cl$ formed upon liberation of the Ti^{IV} metal ion from the pinacolate with TMSCl. It is nevertheless noteworthy that such side reactions were not reported in the previous ketyl cyclizations using this reagent.

Mechanistic Aspects of the Sm^{II}-Promoted Ketyl Cyclization. A possible mechanistic scenario is depicted

(19) (a) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717. (b) Mazéas, D.; Skrydstrup, T.; Doumeix, O.; Beau, J.-M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1383. (c) Skrydstrup, T.; Mazéas, D.; Elmouchir, M.; Doisneau, G.; Riche, C.; Chiaroni A.; Beau, J.-M. *Chem. Eur. J.* **1997**, *3*, 1342.

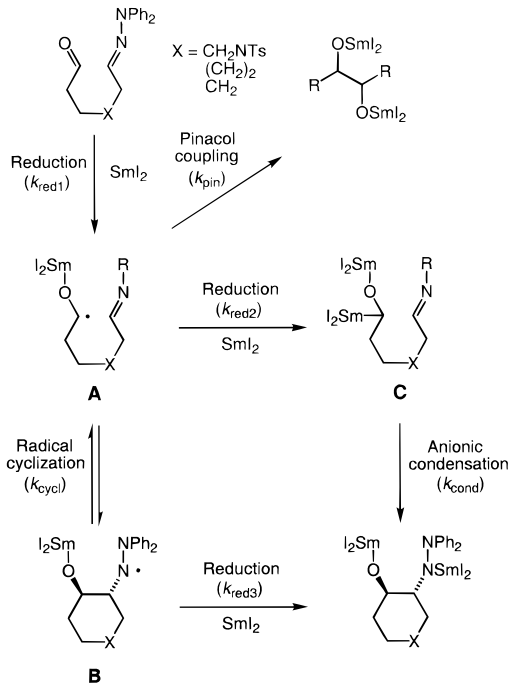
(20) We have recently reported by cyclic voltammetry and conductivity measurements the standard potential ($E°$) for the redox couples SmI_2^+/SmI_2 and $Sm(HMPA)_4^{3+}$ $2I^-/Sm(HMPA)_4^{2+}$ $2I^-$ in THF, found to be −1.43 and −2.23 V vs Fc^+/Fc, respectively. (a) Enemærke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Chem. Commun.* **1999**, 343. (b) Enemærke, R. J.; Hertz, T.; Skrydstrup, T.; Daasbjerg, K. *Chem. Eur. J.*, in press. See also: (c) Shabangi, M.; Kuhlman, R. A.; Flowers, R. A., II. *Org. Lett.* **1999**, *1*, 2133. (d) Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 1137. (e) Shotwell, J. B.; Sealy, J. M.; Flowers, R. A., II. *J. Org. Chem.* **1999**, *64*, 5251.

(21) Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 8157.

(22) Harao, T.; Hatano, B.; Asahara, M.; Muguruma Y.; Ogawa, A. *Tetrahedron Lett.* **1998**, *39*, 5247.

(23) (a) Yamamoto, Y.; Matsumi, D.; Itoh, K. *Chem. Commun.* **1998**, 875. (b) Yamamoto, Y.; Hattori, R.; Itoh, K. *Chem. Commun.* **1999**, 825.

Scheme 5



in Scheme 5. Upon reduction of the aldehyde to a Sm^{III} bound ketyl radical anion **A**,[24] three options are available: (1) ketyl cyclization onto the hydrazone generating an aminyl radical **B** followed by a reduction step; (2) intermolecular pinacol coupling affording the dimeric product; and (3) a two-step reduction of the aldehyde to its dianion **C** followed by an ionic cyclization. Previous kinetic studies by Fallis et al. have demonstrated that secondary alkyl radical additions to the diphenylhydrazones are fast processes with rate constants as high as 1.1×10^8 s^{-1} (80 °C) for the 5-*exo*-cyclization process (*cis*-product) and 9.4×10^5 s^{-1} for the corresponding homologue (6-*exo*).[11b,25] In competition experiments, 5-*exo* and 6-*exo* ketyl-hydrazone cyclizations were found to supersede the corresponding cyclizations onto alkenes by a factor of 25 and 4.2, respectively.[11b] Both the polarization of the C═N bond and the increased stability of the developing nitrogen radical owing to a favorable two-centered, three-electron interaction with the other nitrogen explain these increased cyclization rates. It is therefore plausible that the rate constant for the 7-*exo* cyclization onto the diphenylhydrazones may be of an appreciable size but nevertheless smaller than for both the 5-*exo* and 6-*exo* radical cyclizations. This is indeed confirmed by the isolation of seven-membered ring products upon cyclization of the carbonylhydrazone with SmI_2/HMPA. On the other hand, the 8-*exo* cyclization is probably just too slow to compete with other side reactions.

The facts that successful ketyl-olefin ring closures of up to eight-membered rings have been reported with SmI_2/HMPA[26] and the radical cyclizations onto hydrazones and oximes are faster than for the corresponding unactivated alkenes[11b] suggest that anionic cyclizations with **C** may not be participating at all. The results obtained upon the treatment of the carbonylhydrazone **5** with $SmCl_2$ or $SmBr_2$ (Table 2, entries 5 and 6) lend support to this hypothesis. Under these high reducing conditions, the ketyl intermediate **A** undergoes a second reduction step to the corresponding anion **C**, which apparently will not cyclize and therefore is subsequently protonated, affording the primary alcohol.

Ketyl addition to hydrazones may be reversible reactions (**A** ↔ **B**, Scheme 5), in analogy to both the intramolecular alkyl radical addition and opening of the 5-pentanal and 6-hexanal radicals,[27] as well as ketyl addition to ketones.[10b] If so, it may be expected that the hydrazine radical intermediate would be reduced more effectively under the higher reducing conditions with SmI_2/HMPA and faster than the competing pinacol coupling of the ketyl. On the other hand, with the poorer reducing agent, SmI_2 alone, where the standard potential $E°$ for the redox couple SmI_2^+/SmI_2 is approximately 800 mV more positive than for equivalent redox couple with SmI_2 complexed with HMPA (4 equiv),[20] the pinacol coupling step dominates.[28]

Another plausible mechanism may be considered in which the ratio k_{cycl}/k_{pin} is greatly influenced by the addition of HMPA to the reaction mixtures, thus resulting in the observed divergence of product formation. In the ketyl-alkene cyclizations, Molander suggests the steric bulk around the ketyl oxygen is increased by HMPA complexation with the metal center, hence increasing the persistence of the ketyl and defavoring intermolecular side reactions.[26] This may also explain the observed reduction product obtained when subjecting the carbonylhydrazone **5** to $SmBr_2$ or $SmCl_2$. A second explanation may lie in the reactivity difference between the two ketyl radical anions. It has been well established in electrochemical reductions of aromatic compounds containing carbonyl groups that the rate of pinacol dimerization is substantially increased upon hydrogen-bonding with the ketyl radical anion.[29] For example, in the pinacol coupling of 3-chloroacetophenone, the rate constant in THF was measured to be 1.0×10^3 M^{-1} s^{-1}, whereas with added water an increase to 1×10^4 M^{-1} s^{-1} (100 mM H_2O) and $>1 \times 10^7$ M^{-1} s^{-1} (1 M H_2O) was observed.[29d,e,30] This rate enhancement is explained by an increased spin density at the carbon center of the ketyl upon protonation, as well as reduced electrostatic repulsions in the transition state of the dimerization. Hence, the more anionic character of the ketyl, the slower the dimerization process. A weaker Sm−O bond would probably be expected in the $samarium^{III}$ ketyl complexed with

(24) The hydrazone does not react with either SmI_2 nor SmI_2/HMPA even after prolonged periods (several hours).

(25) Tauh, P.; Fallis, A. G. *J. Org. Chem.* **1999**, *64*, 6960.

(26) 8-*endo* ketyl-olefin cyclizations: (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186. (b) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 789.

(27) (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102. (b) Tsang, R.; Dickson, J. K. Jr.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484. (c) Beckwith, A. L. J.; Hay, B. J. *J. Am. Chem. Soc.* **1989**, *111*, 230. (d) Beckwith, A. L. J.; Hay, B. J. *J. Am. Chem. Soc.* **1989**, *111*, 2674.

(28) Of course, a direct comparison between the difference of the $E°$ of the redox couples SmI_2^+/SmI_2 and $Sm(HMPA)_4^{3+}$ $2I^-/Sm(HMPA)_4^{2+}$ $2I^-$ with the difference in the rates of reduction of the nitrogen radical intermediates cannot be made, as the latter process most likely involves an inner-sphere electron transfer.

(29) (a) Lamy, E.; Nadjo, L.; Savéant, J.-M. *J. Electroanal. Chem.* **1974**, *61*, 141. (b) Savéant, J.-M.; Tessier, D. *J. Electroanal. Chem.* **1975**, *61*, 251. (c) Fussing, I.; Güllü, M.; Hammerich, O.; Husaain, A.; Nielsen, M. F.; Utley, J. H. P. J. Chem. Soc., Perkin Trans 2 1996, 649. (d) Jensen, H.; Daasbjerg, K. *Acta Chem. Scand.* **1998**, *52*, 1151. (e) Daasbjerg, K., personal communication.

(30) The rate constants for the dimerization of both the free and protonated ketyl of benzaldehyde has been measured ($PhCHO^{\bullet -}$, 2.0×10^5 M^{-1} s^{-1}; $PhCHOH^{\bullet}$, $\sim 10^9$ M^{-1} s^{-1}). Andrieux, C. P.; Grzeszczuk, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1991**, *113*, 8811.

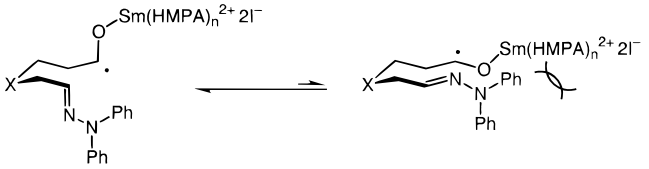


Figure 2. Single-crystal X-ray structure of the hexahydroazepine **26**.

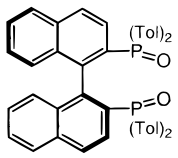
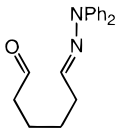
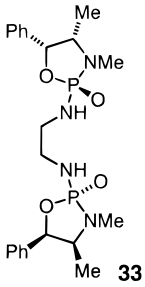
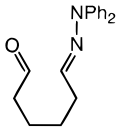
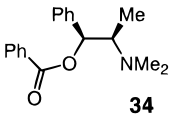
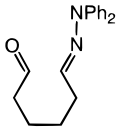
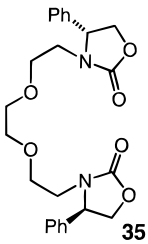
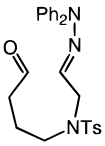
HMPA compared to the uncomplexed species, owing to the strong electron-donating abilities of this ligand. The former complex would therefore display more anionic character at the oxygen, resulting in the generation of a more persistent ketyl with $k_{pin(SmI2/HMPA)} < k_{pin(SmI2)}$. In addition, as the electrostatic interactions are less important for ketyl-hydrazone addition reactions than for the dimerization, the cyclization rates may not be influenced as greatly upon addition of HMPA. With $SmCl_2$, $SmBr_2$ and SmI_2, a tighter Sm−O bond would be anticipated, resulting in a greater spin density at the ketyl carbon center. The slow cyclization event, in particular for the 7-*exo* ring formation, cannot compete with the fast intermolecular pinacol coupling when employing SmI_2. The high reducing conditions with $SmCl_2$ and $SmBr_2$, however, would result in the quick reduction of the ketyl before the pinacol dimerization.

Finally, the observation that cyclization of **4** with SmI_2 leads to a low *trans*:*cis* ratio is inconsistent with a chelated model (Scheme 1).[11a] The Lewis acid ability of the samarium^{III} metal ion is anticipated to be greater in the absence of HMPA, thus favoring a chelated intermediate. Instead, the presence of the complexing agent may simply just increase the sterical interaction between the Sm^{III}-ketyl[26,31] with the large diphenylhydrazone substitutent, forcing the two substituents to adopt pseudoaxial orientations in the transition state rather than the opposing equatorial (Figure 2). A similar explanation has recently been put forth by Chiara and co-workers in their work on the cyclization of carbohydrate-based carbonyloximes to form five-membered ring systems,[14j] as well as Itoh et al. in their *trans*-selective Cp_2TiPh-promoted pinacol cyclizations.[23b]

Attempts At Developing An Enantioselective Ketyl-Hydrazone Cyclization. To develop an asymmetric version of the pinacol-type cyclization, we investigated the possibility of adding chiral complexing agents to SmI_2 prior to the addition of the carbonylhydrazone.[32] It was hypothesized that such ligands would screen the one face of the ketyl intermediate, hence biasing the direction of radical attack onto the hydrazone. With the above results in hand, it became clear that for successful cyclization to occur, such chiral ligands must display strong electron-donating abilities, similar to HMPA.

Table 3 displays some of the ligands tested with the carbonylhydrazone **4** and **16**. In all cases, equimolar amounts of ligands **32**,[32c] **33**,[33] **34**, and **35**[34] were premixed with a THF solution of SmI_2 for approximately 30 min before the ketyl precursor was added. Of the four ligands examined, only **33** (entry 2) showed visible signs of complexation to the divalent lanthanide ion with a change of the solution color from blue to purple, essentially as observed with HMPA. This was also manifested in the subsequent cyclization studies where the ligand **33** promoted rapid ring formation affording **21** in the highest yield yet obtained for this event (entry 2). Nevertheless, this reaction was characterized by a surprisingly poor diastereoselectivity, despite its closest resemblance to HMPA, and essentially no asymmetric induction. With ligands **32**, **34**, and **35** (entries 1, 3, and 4), formation of the cyclic amino alcohol **21** or **23** was slow (approximately 15−30 min) and low yielding, indicative of their poor electron-donating capacities. It is not clear whether the ligands were coordinated at all to either the divalent or trivalent metal ion, but both the diastereo- and enantioselectivities were low or nonexistent, respectively.

Table 3. Cyclization Studies with Chiral Ligands

Entry	Chiral Ligand	Carbonyl -hydrazone	Cyclization Yield (e.e.)
1	 **32**	 **4**	15% (10%)
2	 **33**	 **4**	62% *trans* (5%) 15% *cis*
3	 **34**	 **4**	9% *trans* (0%) 4% *cis*
4	 **35**	 **16**	34% intermolecular pinacol product

Conclusions

The work described herein has shed some light onto the role of HMPA in the samarium iodide induced pinacol-type coupling of carbonylhydrazones. The electron-donating ligand appears to promote the ketyl-hydrazone cyclization for the formation of six- and seven-membered cyclic amino alcohols by modulating the rate constants for the ring formation and the competing intermolecular

(31) (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872.

(32) For some recent examples on asymmetric synthesis with SmI_2, see: (a) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265. (b) Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482. (c) Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1997**, *38*, 1137.

(33) Yang, W.-B.; Fang, J.-M. *J. Org. Chem.* **1998**, *63*, 1356.

(34) Ligands **24** and **25** were designed based on the known strong binding interactions of amides with SmI_2 in other systems.[32a,b]

pinacol coupling, a side reaction that predominates in the absense of HMPA. This reaction has been applied successfully to the synthesis of the fully functionalized hexahydroazepine ring of balanol in racemic form. Our intial investigations using chiral complexing agents suggest the use of strong donating ligands which resemble HMPA in structure. This study is currently ongoing and will be reported in due course.

Experimental Procedure

General Considerations. Unless otherwise stated, all reactions were carried out under argon. THF was dried and freshly distilled over sodium/benzophenone. Dichloromethane was freshly distilled over P_2O_5. Reactions were monitored by thin-layer chromatography (TLC) analysis. The enantiomeric excess measured on compound **21** in the cyclization studies employing chiral ligands was performed using chiral chromatography (Chiral Pack AD column) eluting with hexane/2-propanol (99/1, v/v). The following compounds were prepared according to literature procedures: carbonylhydrazone **4**[11a] and ligand **33**.[33]

2-(*N*′,*N*′-Diphenylhydrazino)cycloheptanol (22). General Procedure for the Cyclization Reactions with SmI_2/HMPA. The aldehyde **6** (89 mg, 0.30 mmol) in a dry flask flushed with argon was dissolved in THF (5 mL) and HMPA (500 μL, 2.86 mmol). To this solution was added a 0.1 M solution of SmI_2 in THF (12.0 mL, 1.20 mmol) at 20 °C. After a few minutes of stirring the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The resulting mixture was diluted with ethyl acetate and the organic phase was washed with water. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Further purification was affected by flash chromatography on silica gel deactivated by washing first with a 1% solution of Et_3N added to the eluting solution (petroleum ether/EtOAc, 9:1). This afforded 51 mg (57%) of the cyclization product **22** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23−1.90 (m, 10H), 1.95 (d, 1H, J = 4.0 Hz), 2.83 (dt, 1H, J = 3.5, 7.2 Hz), 3.68 (tt, 1H, J = 4.0, 7.2 Hz) 6.95−7.06 (m, 2H), 7.14−7.37 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2, 23.1, 27.0, 27.7, 34.6, 63.5, 68.6, 119.9 (4C), 121.7 (2C), 128.5 (4C), 147.5 (2C); MS (electrospray) m/z 319 (M + Na); HRMS: m/e calcd for $C_{19}H_{24}N_2NaO$ (M + Na), 319.1786; found, 319.1787.

3-(*N*′,*N*′-Diphenylhydrazino)-1-(toluene-4-sulfonyl)azepin-4-ol (23). The hexahydroazepine **23** was prepared from carbonylhydrazone **16** according to the general procedure outlined for **22**, with the following quantities: aldehyde **16** (90 mg, 0.20 mmol) in THF (2 mL), 0.1 M SmI_2 in THF (8.0 mL, 0.80 mmol) and HMPA (278 μL, 1.60 mmol). Flash chromatography (petroleum ether/EtOAc, 7:5), afforded **23** (50 mg, 56%) as a colorless oil. ***trans*-Product:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24−1.79 (m, 4H), 2.38 (s, 3H), 2.73 (dd, 1H, J = 9.4, 14.6 Hz), 2.99 (dt, 1H, J = 3.2, 9.4 Hz), 3.01 (m, 1H), 3.46 (m, 2H), 3.91 (dd, 1H, J = 3.2, 14.6 Hz), 4.61 (s, 1H), 6.98−7.11 (m, 2H), 7.13−7.38 (m, 10H), 7.48−7.57 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 22.1, 32.4, 45.0, 47.4, 64.7, 74.8, 121.1 (4C), 122.8 (2C), 127.2 (2C), 129.4 (4C), 129.8 (2C), 135.8, 143.3, 148.6 (2C); MS (electrospray) m/z 474 (M + Na). HRMS: m/e calcd for $C_{25}H_{29}N_3NaO_3S$ (M+Na), 474.1827; found, 474.1829. ***cis*-Product:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52−1.78 (m, 2H), 1.94−2.08 (m, 2H), 2.40 (s, 3H), 2.49 (s, 1H), 3.01 (ddd, 1H, J = 4.4, 6.2, 12.0 Hz), 3.05 (dd, 1H, J = 9.4, 14.0 Hz), 3.25 (dt, 1H, J = 2.6, 9.4 Hz), 3.52 (ddd, 1H, J = 9.4, 6.2, 15 Hz), 3.63 (m, 1H), 3.96 (s, 1H), 4.05 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 21.7, 29.0, 43.7, 47.9, 63.0, 67.8, 120.9 (4C), 123.4 (2C), 127.1 (2C), 129.6 (4C), 129.9 (2C), 136.1 (2C), 143.3 (2C), 148.5 (2C).

3-(2-Benzyloxyaminoethyl)-1-(toluene-4-sulfonyl)azepin-4-ol (24). The hexahydroazepine **24** was prepared from carbonyloxime **20** according to the general procedure outlined for **22**, with the following quantities: aldehyde **20** (49 mg, 0.13 mmol) in THF (5 mL), 0.1 M SmI_2 in THF (5.1 mL, 0.51 mmol) and HMPA (220 μL, 1.26 mmol). Flash chromatography (petroleum ether/EtOAc, 7:5), afforded **24** (25 mg, 40%) as a colorless oil and as an inseparable 5:1 mixture of *trans*:*cis* isomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.51−2.02 (m, 4H), 2.42 (s, 3H), 2.90 (dt, 1H, J = 5.0, 8.6 Hz), 3.06 (ddd, 1H, J = 5.0, 10.8, 12.6 Hz), 3.25−3.65 (m, 4H), 4.71 (s, 2H), 7.25−7.41 (m, 7H), 7.65 (d, 2H, J = 8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 24.8, 31.5, 47.4, 49.7, 53.6, 67.7, 72.9, 127.2 (2C), 128.2, 128.5, 128.6 (2C), 128.8 (2C), 129.9 (2C), 136.1, 137.9; MS (electrospray) m/z 413 (M + Na). HRMS: m/e calcd for $C_{20}H_{26}N_2NaO_4S$ (M + Na), 413.1511; found, 413.1515.

Balanols Hexahydroazepine Fragment 26. A mixture of the cyclization product **23** (95 mg, 0.21 mmol), camphorsulfonic acid (110 mg, 0.44 mmol) and Pearlman's reagent (20% $Pd(OH)_2$/C) (100 mg) in methanol (6 mL) was left overnight in an autoclave at 40 bar of H_2. The reaction mixture was filtered, diluted with CH_2Cl_2 and then washed with an aqueous solution of NaOH (0.2 M) and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The resulting oil was redissolved in dry CH_2Cl_2, whereafter Et_3N (154 μL, 1.11 mmol), *p*-benzyloxybenzoyl chloride (52 mg, 0.21 mmol) and DMAP (2 mg) were added. The reaction mixture was allowed to stir overnight and then washed with water and brine, dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography (petroleum ether/EtOAc, 2:1) yielded 50 mg (48%) of a solid, which could be recrystallized from petroleum ether/ethyl acetate, affording **26** as colorless needles: mp 166−167 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65−2.05 (m, 4H), 2.45 (s, 3H), 2.54−2.70 (m, 1H), 3.15 (dd, 1H, J = 2.6, 15.8 Hz), 3.70 (d, 1H, J = 15.8 Hz), 3.84−4.06 (m, 3H), 4.88 (s, 1H), 5.13 (s, 2H), 7.04 (d, 2H, J = 8.8 Hz), 7.33−7.46 (m, 7H), 7.69 (d, 2H, J = 8.6 Hz), 7.82 (d, 2H, J = 8.8 Hz), 8.03 (d, 1H, J = 4.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.8, 226.1, 31.5, 50.2, 51.6, 58.2, 70.3, 77.6, 115.0 (2C), 125.9, 127.2 (2C), 127.7 (2C), 128.3, 128.9 (2C), 129.4 (2C), 130.2 (2C), 135.0, 136.5, 144.3, 161.9, 168.4; MS (electrospray) m/z 517 (M + Na). HRMS: m/e calcd for $C_{27}H_{30}N_2NaO_5S$ (M + Na), 517.1773; found, 517.1776.

1,14-Bis(*N*′,*N*′-diphenylhydrazono)tetradecane-7,8-diol (28). General Procedure for the Intermolecular Pinacol Coupling. A 0.1 M solution of SmI_2 in THF (8.5 mL, 0.85 mmol) was added to the aldehyde **6** (109 mg, 0.37 mmol) in a dry flask flushed with argon. Workup was affected by quenching with saturated aqueous $NaHCO_3$ after TLC analysis indicated the consumption of starting material (less than 15 min). The resulting mixture was diluted with ethyl acetate and washed with water. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were then washed with brine, dried over magnesium sulfate and concentrated in vacuo. Further purification was affected by flash chromatography on silica gel deactivated by washing first with a 1% solution of Et_3N added to the eluting solution (petroleum ether/EtOAc, 3:1). The pinacol product **28** was obtained as a colorless syrup (61 mg, 56%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22−1.61 (m, 16H), 1.82 (m, 1H), 1.98 (m, 1H), 2.27 (dt, 4H, J = 5.6, 7.2 Hz), 3.38 (m, 1H), 3.58 (m, 1H), 6.52 (t, 2H, J = 5.6 Hz), 7.04−7.15 (m, 12H), 7.31−7.41 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.4, 26.9, 28.9, 32.6 (4C), 62.9, 122.2 (8C), 123.7 (4C), 129.6 (8C), 140.0 (4C), 144.2; MS (electrospray) m/z 613 (M + Na). HRMS: m/e calcd for $C_{38}H_{46}N_4NaO_4$ (M + Na), 613.3518; found, 613.3519.

1,12-Bis(*N*′,*N*′-diphenylhydrazono)dodecane-6,7-diol (27). The diol **27** was prepared from carbonylhydrazone **4** according to the general procedure outlined for **28**, with the following quantities: aldehyde **4** (74.4 mg, 0.27 mmol) and 0.1 M solution of SmI_2 in THF (10.6 mL, 1.06 mmol). Flash chromatography (petroleum ether/EtOAc, 2:1) afforded **27** (29 mg, 39%) as a colorless syrup along with the cyclized product **21** (7.2 mg, 10%) as a 4:1 mixture of *trans*:*cis* isomers. For **27**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22−1.62 (m, 12H), 1.84 (m, 1H), 2.02 (m, 1H), 2.29 (dt, 4H, J = 5.4, 7.2 Hz), 3.39 (m, 1H), 3.59 (m, 1H), 6.52 (t, 2H, J = 5.4 Hz), 7.03−7.15 (m, 12H), 7.31−7.40 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.4, 25.8, 27.2, 31.2, 32.8, 33.5, 74.6, 74.7, 122.5 (4C), 124.1 (2C), 129.9

(4C), 140.0, 144.5 (2C); MS (electrospray) *m*/*z* 585 (M + Na). HRMS: *m*/*e* calcd for $C_{36}H_{42}N_4NaO_2$ (M + Na), 585.3205; found, 585.3217. For *trans*-**21**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18−1.38 (m, 4H), 1.57−1.76 (m, 2H), 1.86−2.01 (m, 2H), 2.40 (bs, 1H), 2.74 (dt, 1H, J = 3.9, 9.7 Hz), 3.68 (dt, 1H, J = 4.8, 9.7 Hz), 6.95−7.06 (m, 2H), 7.14−7.37 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.5, 23.8, 28.9, 33.5, 60.6, 73.9, 120.0 (4C), 121.9 (2C), 128.5 (4C), 147.7 (2C); MS (electrospray) *m*/*z* 305 (M + Na). For *cis*-**21**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20−1.81 (m, 7H), 1.96 (m, 1H), 2.55 (s, 1H), 2.96 (ddd, 1H, J = 2.6, 4.6, 10.4 Hz), 3.90 (s, 1H), 4.02 (m, 1H), 6.97−7.14 (m, 6H), 7.25−7.35 (m, 4H); MS (electrospray) *m*/*z* 305 (M + Na).

***N*-(2-(*N*′,*N*′-Diphenylhydrazono)ethyl)-*N*-(8-((2-(*N*′,*N*′-diphenylhydrazono)ethyl)benzenesulfonylamino)-4,5-dihydroxyoctyl)benzenesulfonamide (29).** The diol **29** was prepared from carbonylhydrazone **16** according to the general procedure outlined for **28**, with the following quantities: aldehyde **16** (100 mg, 0.22 mmol) and 0.1 M solution of SmI_2 in THF (8.9 mL, 0.89 mmol). Flash chromatography (petroleum ether/EtOAc, 7:5) afforded **29** (69 mg, 69%) as a colorless syrup: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35−1.81, (m, 8H), 1.91 (d, 1H, J = 3.8 Hz), 2.13 (d, 1H, J = 3.8 Hz), 2.40 (s, 6H), 3.14 (t, 4H, J = 7.2 Hz), 3.34 (m, 1H), 3.51 (m, 1H), 4.00 (d, 4H, J = 5.6 Hz), 6.20 (t, 2H, J = 5.6 Hz), 6.95−7.01 (m, 8H), 7.10−7.39 (m, 16H), 7.59−7.64 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0, 25.8, 29.5, 47.0, 49.2, 73.3, 121.5 (8C), 123.9 (4C), 126.4 (4C), 129.1 (4C), 129.2 (8C), 131.6, 135.9, 142.6, 142.6 (4C); MS (electrospray) *m*/*z* 923 (M + Na). HRMS: *m*/*e* calcd for $C_{50}H_{56}N_6NaO_6S_2$ (M + Na), 923.3600; found, 923.3599.

***N*-(2-Benzyloxyiminoethyl)-*N*-(8-((2-benzyloxyiminoethyl)benzenesulfonylamino)-4,5-dihydroxyoctyl)benzenesulfonamide (30).** The diol **30** was prepared from carbonyloxime **20** according to the general procedure outlined for **28**, with the following quantities: aldehyde **20** (80 mg, 0.21 mmol) and 0.1 M solution of SmI_2 in THF (8.2 mL, 0.82 mmol). Flash chromatography (petroleum ether/EtOAc, 7:5) afforded **30** (44 mg, 50%) as a colorless syrup: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30−1.80 (m, 8H), 2.41 (s, 6H), 3.15 (m, 8H), 3.86 (d, 2H, J = 6.2 Hz), 4.04 (d, 2H, J = 4.2 Hz), 5.02 (s, 2H), 5.09 (s, 2H), 6.64 (t, 1H, J = 4.3 Hz), 7.22−7.40 (m, 15H), 7.66 (dd, 4H, J = 1.2, 8.2 Hz); MS (electrospray) *m*/*z* 801 (M + Na). HRMS: *m*/*e* calcd for $C_{40}H_{50}N_4NaO_8S_2$ (M + Na), 801.2968; found, 801.3013.

***N*-(2-(*N*′,*N*′-Diphenylhydrazono)ethyl)-*N*-(4-hydroxy-4-phenylbutyl)-4-methylbenzenesulfonamide (31).** To a solution of the Cp_2TiCl_2 (100 mg, 0.40 mmol) in THF (1.5 mL) under argon was added a 2.0 M solution of isopropylmagnesium bromide in THF (170 μL, 0.40 mmol) at 20 °C. A 1.0 M solution of phenylmagnesium bromide in THF (450 μL, 0.40 mmol) was added to the resulting green solution and the reaction mixture was stirred for 30 min. The carbonylhydrazone **16** (60 mg, 0.13 mmol) in THF (0.5 mL) was then added and the reaction mixture was left stirring overnight. TLC analysis showed no consumption of **16**, hence TMSCl (17 μL, 0.13 mmol) was injected. Again no consumption of **16** was observed by TLC analysis, and therefore 3 equiv of benzaldehyde were added to test the reactivity of the Cp_2TiPh formed. After 30 min, **16** was completely consumed and the reaction mixture was quenched with saturated aqueous NH_4Cl. CH_2Cl_2 was added and the organic phase was washed once with water, then dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography (petroleum ether/EtOAc, 3:1) yielded 37 mg (53%) of **31** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50−1.81 (m, 4H), 2.38 (s, 3H), 2.92 (broad s, 1H), 3.16 (m, 2H), 4.00 (d, 2H, J = 5.6 Hz), 4.67 (m, 1H), 6.19 (t, 1H, J = 5.6 Hz), 6.90−7.00 (m, 4H), 7.08−7.40 (m 13H), 7.55−6.64 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.8, 24.8, 35.9, 47.9, 50.1, 62.5, 74.2, 79.3, 122.3, 124.7, 126.0, 127.1, 127.2, 127.8, 128.1, 128.3, 128.7, 129.9, 130.0, 132.4, 136.7, 140.1, 143.4, 144.6; MS (electrospray) *m*/*z* 550 (M + Na). HRMS: *m*/*e* calcd for $C_{31}H_{33}N_3NaO_3S$ (M + Na), 550.2131; found, 550.2131.

Cyclization of Carbonylhydrazone 4 with Ligand 33. A 0.1 M solution of SmI_2 in THF (6.3 mL, 0.63 mmol) was added to the ligand **33** (300 mg, 0.63 mmol) in a dry flask flushed with argon. After stirring for 10 min, a solution of the carbonylhydrazone **4** (59 mg, 0.21 mmol) in THF (3 mL) was added at 20 °C. After a few minutes of stirring, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The resulting mixture was diluted with ethyl acetate and the organic phase was washed with water. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Further purification was affected by flash chromatography on silica gel deactivated by washing first with a 1% solution of Et_3N added to the eluting solution (petroleum ether/EtOAc, 9:1). This afforded a 4:1 mixture of *trans*-**21** (37.2 mg) and *cis*-**21** (9.4 mg) with a combined yield of 77%.

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Supporting Information Available: Single-crystal X-ray structure and crystallographic data of the hexahydroazepine **26**, experimental procedures and characterization of compounds **2**, **5**, **6**, **8**−**11**, and **15**−**20**, and ^{1}H NMR spectra for compounds **5**, **6**, **8**−**11**, **15**−**24**, and **26**−**31**. This material is available free of charge via the Internet at http//pubs.acs.org.

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