

Synthetic Methods

Selective Reduction of Barbituric Acids Using $\text{SmI}_2/\text{H}_2\text{O}$: Synthesis, Reactivity, and Structural Analysis of Tetrahedral Adducts**

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Since the 1864 landmark discovery by Adolf von Baeyer,^[1] barbituric acids have played a prominent role in medicine and organic synthesis. The barbituric acid scaffold occurs in more than 5000 pharmacologically active compounds, including commonly used anticonvulsant, hypnotic, and anticancer agents (Figure 1a).^[2] Moreover, as an easily accessible feed-stock material, it is an extremely useful building block for organic synthesis.^[3] However, despite the fact that barbiturates have been extensively studied for over a century, the general monoreduction of barbituric acids remains unknown,^[4] even though it would have considerable potential for the production and discovery of pharmaceuticals, materials, and polymers. Interestingly, the barbiturate monoreduction products would formally constitute a new class of tetrahedral intermediates of amide bond addition reactions, only few of which have been successfully isolated to date because of their transient nature.^[5]

Single-electron-transfer reactions open up unexplored reaction space charted with chemoselectivity and reactivity levels difficult to access by ionic reaction mechanisms.^[6] The generation of ketyl-type radicals with SmI_2 is particularly valuable in this regard because of the excellent chemoselectivity imparted by the reagent and the potential to effect polarity reversal of the carbonyl group through a single-electron-reduction event (Figure 1b).^[7,8] However, the selective reduction of amide carbonyls with SmI_2 is challenging and no general method to achieve this highly desirable transformation is currently available.^[9]

Herein, we demonstrate that the $\text{SmI}_2/\text{H}_2\text{O}$ reagent^[10] can perform the selective monoreduction of barbituric acids to the corresponding hemiaminals (Figure 1c). To our knowledge these are the first general examples of monoreduction of such systems^[4] as well as the reduction of amide-type

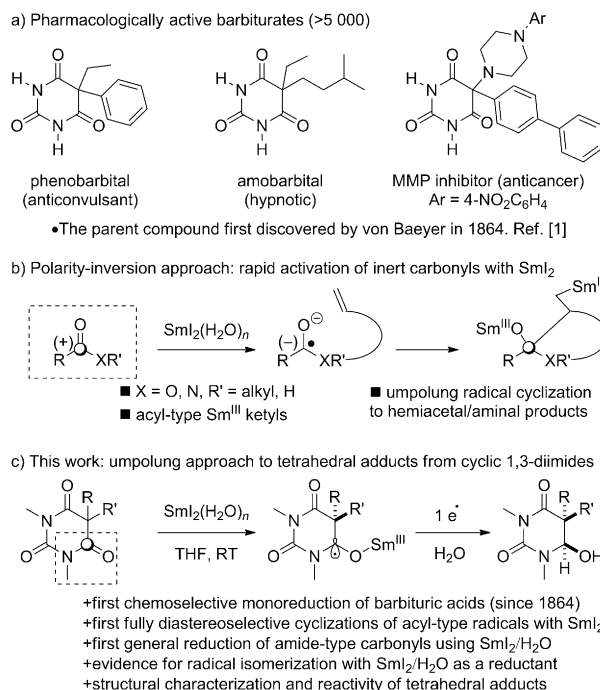


Figure 1. a) Examples of pharmacologically active barbiturates. b) Polarity inversion strategy using SET approach. c) This study.

carbonyls with SmI_2 .^[7,8] The hemiaminal products are analogous to tetrahedral intermediates derived from amide addition reactions.^[5] Moreover, the radical intermediates formed by the one-electron reduction have been utilized in intramolecular additions to alkenes. For the first time in any SmI_2 -mediated cross-couplings of acyl-type radicals,^[11] these additions proceed with full control of diastereoselectivity.^[12] Furthermore, experimental evidence is provided for the isomerization of vinyl radical intermediates under $\text{SmI}_2/\text{H}_2\text{O}$ reaction conditions. This discovery opens the door for the use of $\text{SmI}_2/\text{H}_2\text{O}$ in cascade reductive processes employing C-centered radicals.^[13] Overall, these studies provide a basis for multiple methodologies to form versatile hemiaminal products (cf. hemiacetals) by a formal amide polarity reversal event.^[6]

We hypothesized that single-electron reduction of barbituric acids (cyclic 1,3-diimides) to their respective radical anions could provide a benchmark for the development of a general system for the reduction of a wide range of amide functional groups. We considered that 1) in the barbituric acid system the reduction of one of the imide carbonyls would be enhanced because of its lower energy π^*_{CO} orbital, 2) the reduction would be favored by anomeric stabilization of the radical anion intermediate, and 3) the $n_{\text{N}} \rightarrow \pi^*_{\text{CO}}$ delocaliza-

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tion into the remaining carbonyl in a conformationally locked system would provide access to stable, and unusual, hemiaminal products.

After extensive optimization of the reaction conditions, we determined that barbituric acids are reduced with $\text{SmI}_2/\text{H}_2\text{O}$ to the corresponding hemiaminals in good yields and diastereoselectivities (Table 1). Typically, a twofold excess of

Table 1: Reduction of barbituric acids using SmI_2 .^[a]

Entry	1,3-Diimide	Product	Yield [%]	d.r. [%]
1	1a , R = <i>i</i> Bu	2a	83	88:12
2	1b , R = $\text{C}_{10}\text{H}_{21}$	2b	56	86:14
3	1c , R = $(\text{CH}_2)_2\text{iPr}$	2c	80	91:9
4	1d , R = $(\text{CH}_2)_2\text{Ph}$	2d	75	88:12
5	1e , R = $(\text{CH}_2)_2\text{CHMePh}$	2e	78	85:15
6	1f , X = MeO	2f	80	88:12
7	1g , X = CF_3	2g	76	85:15
8	1h , X = Br	2h	67	87:13
9	1i , R ¹ = Me, R ² = $\text{C}_{10}\text{H}_{21}$	2i	71	77:23
10	1j , R ¹ = Me, R ² = <i>i</i> Bu	2j	50	87:13
11	1k , R ¹ , R ² = $(\text{CH}_2)_2\text{CH}=\text{CH}(\text{CH}_2)_2$	2k	55	—
12 ^[b]	1l , R ¹ , R ² = $=\text{C}(\text{OH})\text{Bn}$	2l	76	87:13
13 ^[b]	1m , R ¹ , R ² = $=\text{CHiPr}$	2m	58	88:12

[a] Reaction conditions: SmI_2 (4 equiv), THF, H_2O , 10–60 s. [b] Reaction conditions: SmI_2 (6–8 equiv), THF, H_2O , 10–60 s. See the Supporting Information for full experimental details. THF = tetrahydrofuran.

reagent was used to ensure that the reactions were complete. A wide range of substrates exhibited excellent reactivity, including those with sensitive α protons (entries 1–8), as well as those with sterically hindered quaternary centers (entries 9–11). Importantly, the method tolerates functional groups that are typically reduced under single-electron-transfer conditions, including aromatic rings (entries 4 and 5), ethers (entry 6), trifluoromethyl groups (entry 7), and halides (entry 8). The potential of the reaction to streamline synthetic routes by sequential reductive processes has also been demonstrated (entries 12 and 13). Several products bear close analogy to the pharmacologically active barbiturates (entry 3: amobarbital, entry 10: butalbital).

We determined that the use of H_2O is critical for the observed reactivity, which is in line with the formation of a more thermodynamically powerful reductant required to activate amide-type carbonyls.^[14] No over-reduction is seen, even in the presence of excess reagent. Other SmI_2 -based

systems,^[15] including reductants with a higher redox potential than $\text{SmI}_2/\text{H}_2\text{O}$, such as those with alcohols (MeOH , $t\text{BuOH}$, EG), Lewis bases (HMPA, Et_3N), or salts (LiCl) did not provide the desired products.^[15] Competition experiments (see the Supporting Information) illustrate that $\text{SmI}_2/\text{H}_2\text{O}$ is selective for cyclic 1,3-diimides over reactive six-membered lactones, thus suggesting that significant levels of selectivity are possible with this reagent system.

To further evaluate the potential of our method, we examined several substrates bearing an unactivated π system tethered to the barbituric acid scaffold (Table 2). A broad

Table 2: Reductive coupling of barbituric acids using SmI_2 .^[a]

Entry	3	R ¹	R ²	4	Yield [%]	d.r. [%]
1	3a	<i>i</i> Bu	H	4a	74	> 95:5
2	3b	<i>i</i> Bu	Ph	4b	58	> 95:5
3	3c	<i>i</i> Bu	4-MeOC ₆ H ₄	4c	59	> 95:5
4	3d	C_7H_{13}	Ph	4d	64	> 95:5
5	3e	C_4H_7	H	4e	55	> 95:5
6	3f	<i>i</i> Bu	H	4f	63	> 95:5
7	3g	<i>i</i> Bu	TMS	4g	66	> 95:5 ^[b]
8	3h	<i>i</i> Bu	Ph	4h	90	63:37 ^[c]
9	3i	C_4H_5	H	4i	82	> 95:5

[a] Reaction conditions: SmI_2 (6 equiv), THF, H_2O , 1–15 min. See the Supporting Information for full experimental details. [b] *E* isomer; > 95:5 d.r. [c] *Z/E* geometry. TMS = trimethylsilyl.

range of cyclic 1,3-diimides bearing alkene (entries 1–5) and alkyne (entries 6–9) substituents underwent efficient radical cyclizations, thus resulting in the formation of bicyclic hemiaminals in good to excellent yields. For the first time in any radical cyclization mediated by $\text{SmI}_2/\text{H}_2\text{O}$, all products were formed with a high degree of stereoisomeric control around the five-membered ring.^[11] We hypothesize that the increased half-life of the acyl-type radical, stabilized by the $\text{n}_\text{N} \rightarrow \text{SOMO}$ conjugation (cf. esters),^[16] permits the alkene tether to adopt the lowest energy conformation before the cyclization. This finding bodes well for the development of other SmI_2 -promoted radical cyclizations based on amide bond umpolung.

We have carried out preliminary studies to elucidate the mechanism of the reaction (see the Supporting Information for details): 1) The reduction of **1i** with $\text{SmI}_2/\text{D}_2\text{O}$ (> 98% D_1 ; $k_\text{H}/k_\text{D} = 1.5 \pm 0.1$)^[11a] suggests that anions are generated and protonated by H_2O in a series of electron-transfer steps and that proton transfer is not involved in the rate-determining step of the reaction.^[17] 2) Control experiments with a cyclic 1,3-malonamide and DMPU demonstrate that activation of the amide carbonyl facilitates the reaction. 3) Intermolecular competition experiments show that the rate of the reduction

can be modified by steric and electronic substitution at the α -carbon atom. 4) Deuterium incorporation and KIE studies on the reductive cyclizations suggest that proton transfer is not involved in the rate-determining step (Figure 2). 5) The reaction of **3d** to give **[D₁]-4d** (1:1 d.r.) demonstrates that

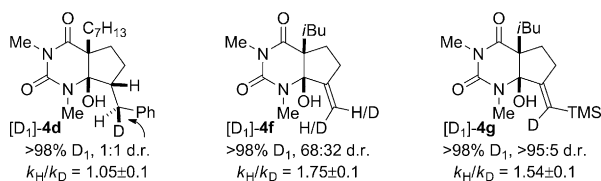
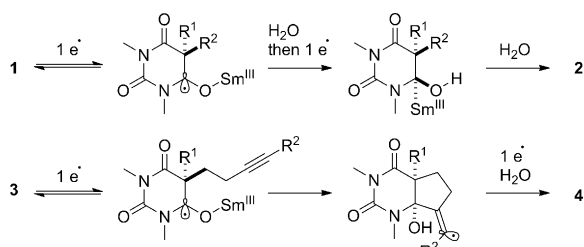


Figure 2. Reductive coupling of barbituric acids **3d**, **3f**, and **3g** using $\text{SmI}_2/\text{D}_2\text{O}$ (only products are shown).

the benzylsamarium(III) intermediate is not coordinated to the hydroxy group (Figure 2).^[11a] 6) The reactions of **3f** and **3g** indicate inversion of the vinyl radical^[18] under the reduction conditions (Figure 2). 7) A gradual change in diastereoselectivity is observed in the cyclizations of **3h** at varied concentrations of H_2O ,^[10] additionally suggesting that the carbon-centered radicals do not undergo instantaneous reduction/protonation.^[14] 8) Finally, intermolecular competition experiments indicate that the rate of the cyclization is governed by electronic and steric properties of the π acceptor,^[19] suggesting significant levels of chemoselectivity in these cyclizations.^[8j]

A proposed mechanism is shown in Scheme 1. We hypothesize that the kinetic diastereoselectivity in the reduction results from the formation of an organosamarium(III) on



Scheme 1. Mechanism of the reduction and cyclization of barbituric acids using $\text{SmI}_2/\text{H}_2\text{O}$.

the less hindered face of the molecule. This is analogous to the classic reduction of cyclic ketones to equatorial alcohols by related $\text{SmI}_2/\text{H}_2\text{O}$ systems.^[10] In the reductive cyclization, the radical anion undergoes an *anti* addition^[20] to give the vinyl radical intermediate, which isomerizes, depending on the steric and electronic preferences of the π acceptor and the reaction conditions. Control experiments (see the Supporting Information) point to the critical role of H_2O in stabilizing the radical anion^[14] and promoting cyclization (no reaction is observed in the absence or at low concentration of H_2O as well as with more powerful SmI_2 -based reductants, SmI_2/LiCl and SmI_2/HMPA).

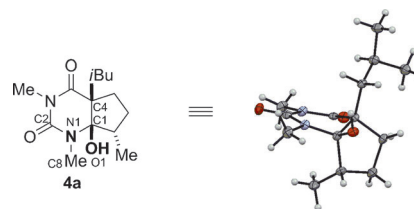
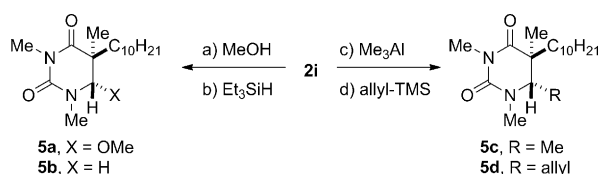


Figure 3. X-ray structure of **4a**. Selected bond lengths [Å] and angles [°]: N1–C1 1.466, C1–O1 1.407, C1–C4 1.552, C1–H1 0.84, N1–C2 1.354, C2–O2 1.218, N2–C2 1.421; C2–N1–C1–O1 155.1, C8–N1–C1–O1 –40.6, N1–C1–O1–H1 –52.1, C4–C1–O1–H1 70.8, C1–N1–C2–N2 –6.9, C2–N2–C3–C4 –14.6, N1–C2–N2–C3 –3.6.^[23]

The α -amino alcohol moiety derived from barbituric acid reduction is stabilized by a nonplanar arrangement of atoms (Figure 3). The X-ray crystal structure of **4a** reveals that the C1–O1 bond (1.407 Å) is shorter than the average $\text{C}_{\text{sp}^3}\text{--O}$ bond (1.432 Å),^[5a] whereas the length of N1–C1 bond is 1.466 Å, which corresponds to a typical $\text{C}_{\text{sp}^3}\text{--N}$ bond (1.469 Å).^[5a] The C1–C4 bond length of 1.552 Å is slightly longer than the average $\text{C}_{\text{sp}^3}\text{--C}_{\text{sp}^3}$ bond (1.530 Å).^[5a] The torsion angle between Nlp (lp = lone pair) and C1–O1 bond of 57.3° is consistent with the absence of $\text{Nlp} \rightarrow \sigma^*_{\text{C–O}}$ interactions. However, there is a good overlap between the O1lp1 and the N1–C1 bond (ca. 172°) and between O1lp2 and the C1–C4 bonds (ca. 191°). The shortened C1–O1 bond and the elongated C1–C4 bond are consistent with an anomeric effect resulting from $\text{Olp1} \rightarrow \sigma^*_{\text{C1–N1}}$ and $\text{Olp2} \rightarrow \sigma^*_{\text{C1–C4}}$ interactions, while the geometry of the N1 atom indicates the beginning of the decomposition of the tetrahedral intermediate by the elimination of N(CO) group. It should be noted that the α -amino alcohol function in this system is stabilized by the reduced $\text{Nlp} \rightarrow \sigma^*_{\text{C1–O1}}$ conjugation because of the interaction of Nlp with the adjacent carbonyl group.

Interestingly, the X-ray structure of the monocyclic analogue **2f** shows kinetic rather than thermodynamic stability (see the Supporting Information). The torsion angles between Nlp and C1–O1 of about 175° and Olp and C1–N1 of about 37° indicate a significant $\text{Nlp} \rightarrow \sigma^*_{\text{C1–O1}}$ interaction in this system, and the absence of $\text{Olp} \rightarrow \sigma^*_{\text{C1–N1}}$ conjugation. The O1–C1–C4–H4 torsion angle of approximately 180° reveals a perfect antiperiplanar arrangement between the α -hydrogen atom and the hydroxy group. These parameters are consistent with the beginning of the decomposition of the α -amino alcohol moiety by the elimination of a hydroxy group to give acyliminium. Overall, these features seem to be characteristic of the α -amino alcohol function stabilized by scaffolding effects in a barbituric acid system and indicate that isolation of a range of analogues can be readily achieved.

Finally, we have preliminary results pertaining to the reactivity of these hemiaminals (Scheme 2). We determined that the alcohol could be directly displaced with a variety of heteroatom and carbon nucleophiles under mild reaction conditions. We also showed that the *N,N*-phenobarbital-derived hemiaminal undergoes an unprecedented 1,2-aryl shift (see the Supporting Information). These results bode



Scheme 2. Reactivity of the tetrahedral adducts **2**. Reaction conditions: a) MeOH, HCl, RT, 3 h, 99%. b) Et₃SiH, BF₃·Et₂O, RT, 3 h, 96%. c) Me₃Al, RT, 3 h, 78%. d) allyl-TMS, BF₃·Et₂O, RT, 2 h, 86%.

well for accessing a wide range of biologically active uracil derivatives.^[21]

In summary, we have developed the first general method for the monoreduction of barbituric acids since their seminal discovery in 1864 by von Baeyer. This reaction constitutes the first general method for the reduction of amide-type carbonyls using SmI₂.^[22] The radicals formed by one-electron reduction of the amide bond have been applied in intramolecular additions to alkenes. The cyclic hemiaminal products are analogous to tetrahedral intermediates derived from amide addition reactions and are formed in a formal polarity reversal event. We fully expect that the present work will provide the basis for the synthesis of novel barbituric acid derivatives and will result in the development of an array of modern synthetic methodologies to access reductive amide umpolung by electron transfer events.

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- [1] a) A. von Baeyer, *Justus Liebigs Ann. Chem.* **1864**, 130, 129; for the first mention of barbituric acid by von Baeyer, see: b) A. von Baeyer, *Justus Liebigs Ann. Chem.* **1863**, 127, 199; selected historical perspectives: c) M. K. Carter, *J. Chem. Educ.* **1951**, 28, 524; d) G. B. Kauffmann, *J. Chem. Educ.* **1980**, 57, 222; e) A. de Meijere, *Angew. Chem.* **2005**, 117, 8046; *Angew. Chem. Int. Ed.* **2005**, 44, 7836; f) A. W. Jones, *Perspectives in Drug Discovery*, Linköping, **2010**.
- [2] Reviews: a) J. T. Bojarski, J. L. Mokrosz, H. J. Barton, M. H. Paluchowska, *Adv. Heterocycl. Chem.* **1985**, 38, 229; b) D. J. Abraham, D. P. Rotella, *Burger's Medicinal Chemistry, Drug Discovery and Development*, Wiley, Hoboken, **2010**; c) F. López-Muñoz, R. Ucha-Udabe, C. Alamo, *Neuropsychiatr. Dis. Treat.* **2005**, 1, 329; d) F. Seeliger, S. T. A. Berger, G. Y. Remennikov, K. Polborn, H. Mayr, *J. Org. Chem.* **2007**, 72, 9170.
- [3] Selected recent applications: a) K. Takenaka, N. Itoh, H. Sasai, *Org. Lett.* **2009**, 11, 1483; b) M. Holzwarth, A. Dieskau, M. Tabassam, B. Plietker, *Angew. Chem.* **2009**, 121, 7387; *Angew. Chem. Int. Ed.* **2009**, 48, 7251; c) S. Fujimori, E. M. Carreira, *Angew. Chem.* **2007**, 119, 5052; *Angew. Chem. Int. Ed.* **2007**, 46, 4964; d) M. U. Schmidt, J. Brüning, J. Glinemann, M. W. Hützel, P. Mörschel, S. N. Ivashevskaya, J. van de Streek, D. Braga, L. Maini, M. R. Chierotti, R. Gobetto, *Angew. Chem.* **2011**, 123, 8070; *Angew. Chem. Int. Ed.* **2011**, 50, 7924; e) K. Mori, S. Sueoka, T. Akiyama, *J. Am. Chem. Soc.* **2011**, 133, 2424; f) S. Reddy Chidipudi, I. Khan, H. W. Lam, *Angew. Chem.* **2012**, 124, 12281; *Angew. Chem. Int. Ed.* **2012**, 51, 12115; g) A. R. Daniewski, W. Liu, M. Okabe, *Org. Process Res. Dev.* **2004**, 8, 411; h) J. C. Ruble, A. R. Hurd, T. A. Johnson, D. A. Sherry, M. R. Barbachyn, P. L. Toogood, G. L. Bundy, D. R. Graber, G. M. Kamilar, *J. Am. Chem. Soc.* **2009**, 131, 3991; i) X. Huang, C. Li, S. Jiang, X. Wang, B. Zhang, M. Liu, *J. Am. Chem. Soc.* **2004**, 126, 1322.
- [4] Ring scission and over-reduction have been observed in reactions with other reductants: a) K. H. Dudley, I. J. Davis, D. K. Kim, F. T. Ross, *J. Org. Chem.* **1970**, 35, 147; b) See, Ref. [2a].
- [5] For reviews, see: a) M. Adler, S. Adler, G. Boche, *J. Phys. Org. Chem.* **2005**, 18, 193; b) P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Elmsford, NY, **1983**; examples of isolated tetrahedral intermediates: c) A. J. Kirby, I. V. Komarov, N. Feeder, *J. Am. Chem. Soc.* **1998**, 120, 7101; d) D. A. Evans, G. Borg, K. A. Scheidt, *Angew. Chem.* **2002**, 114, 3320; *Angew. Chem. Int. Ed.* **2002**, 41, 3188; e) C. Cox, H. Wack, T. Lectka, *J. Am. Chem. Soc.* **1999**, 121, 7963; f) M. Szostak, J. Aubé, *J. Am. Chem. Soc.* **2010**, 132, 2530; g) M. Adler, M. Marsch, N. S. Nudelman, G. Boche, *Angew. Chem.* **1999**, 111, 1345; *Angew. Chem. Int. Ed.* **1999**, 38, 1261.
- [6] Reviews on metal-mediated radical reactions: a) B. M. Trost, I. Fleming, *Comprehensive Organic Synthesis*, Pergamon, New York, **1991**; b) A. Gansäuer, H. Blum, *Chem. Rev.* **2000**, 100, 2771; c) M. Szostak, D. J. Procter, *Angew. Chem.* **2012**, 124, 9372; *Angew. Chem. Int. Ed.* **2012**, 51, 9238; d) "Radicals in Synthesis I and II": A. Gansäuer in *Topics in Current Chemistry*, Vol. 263–264, Springer, Heidelberg, **2006**; an excellent review on reductive umpolung: e) J. Streuff, *Synthesis* **2013**, 45, 281.
- [7] D. J. Procter, R. A. Flowers II, T. Skrydstrup, *Organic Synthesis using Samarium Diodide: A Practical Guide*, RSC Publishing, Cambridge, **2010**.
- [8] For reviews, see: a) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, 96, 307; b) A. Krief, A. M. Laval, *Chem. Rev.* **1999**, 99, 745; c) H. B. Kagan, *Tetrahedron* **2003**, 59, 10351; d) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, 104, 3371; e) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem.* **2009**, 121, 7276; *Angew. Chem. Int. Ed.* **2009**, 48, 7140; f) M. Szostak, D. J. Procter, *Angew. Chem.* **2011**, 123, 7881; *Angew. Chem. Int. Ed.* **2011**, 50, 7737; g) C. Beemelmans, H. U. Reissig, *Chem. Soc. Rev.* **2011**, 40, 2199; h) B. Sautier, D. J. Procter, *Chimia* **2012**, 66, 399; i) M. Szostak, M. Spain, D. J. Procter, *Chem. Soc. Rev.* DOI: 10.1039/c3cs60223k; extremely relevant review about chemo-selective electron transfer using SmI₂.
- [9] Skrydstrup and co-workers reported an elegant coupling of N-acyl oxazolidinones by a radical addition mechanism: a) C. M. Jensen, K. B. Lindsay, R. H. Taaning, J. Karaffa, A. M. Hansen, T. Skrydstrup, *J. Am. Chem. Soc.* **2005**, 127, 6544; b) A. M. Hansen, K. B. Lindsay, P. K. S. Antharjanam, J. Karaffa, K. Daasbjerg, R. A. Flowers II, T. Skrydstrup, *J. Am. Chem. Soc.* **2006**, 128, 9616; c) R. H. Taaning, K. B. Lindsay, B. Schjøtt, K. Daasbjerg, T. Skrydstrup, *J. Am. Chem. Soc.* **2009**, 131, 10253; d) J. P. Ebran, C. M. Jensen, S. A. Johannesen, J. Karaffa, K. B. Lindsay, R. H. Taaning, T. Skrydstrup, *Org. Biomol. Chem.* **2006**, 4, 3553; Namy reported coupling of imides via a fragmentation mechanism: e) S. Farcas, J. L. Namy, *Tetrahedron Lett.* **2000**, 41, 7299; Ha et al. and Farcas and Namy reported the addition of organosamariums to imides: f) D. C. Ha, C. S. Yun, Y. Lee, *J. Org. Chem.* **2000**, 65, 621; g) S. Farcas, J. L. Namy, *Tetrahedron Lett.* **2001**, 42, 879.
- [10] For a recent review, see: M. Szostak, M. Spain, D. Parmar, D. J. Procter, *Chem. Commun.* **2012**, 48, 330.
- [11] For selected studies, see: a) D. Parmar, L. A. Duffy, D. V. Sadasivam, H. Matsubara, P. A. Bradley, R. A. Flowers II, D. J. Procter, *J. Am. Chem. Soc.* **2009**, 131, 15467; b) K. D. Collins, J. M. Oliveira, G. Guazzelli, B. Sautier, S. De Grazia, H. Matsubara, M. Helliwell, D. J. Procter, *Chem. Eur. J.* **2010**, 16, 10240; c) D. Parmar, K. Price, M. Spain, H. Matsubara, P. A.

- Bradley, D. J. Procter, *J. Am. Chem. Soc.* **2011**, *133*, 2418; d) D. Parmar, H. Matsubara, K. Price, M. Spain, D. J. Procter, *J. Am. Chem. Soc.* **2012**, *134*, 12751; e) B. Sautier, S. E. Lyons, M. R. Webb, D. J. Procter, *Org. Lett.* **2012**, *14*, 146.
- [12] For a classic review on Sm^{II}-mediated cascade cyclizations, see: G. A. Molander, C. R. Harris, *Tetrahedron* **1998**, *54*, 3321.
- [13] a) L. A. Duffy, H. Matsubara, D. J. Procter, *J. Am. Chem. Soc.* **2008**, *130*, 1136; b) G. Guazzelli, S. De Grazia, K. D. Collins, H. Matsubara, M. Spain, D. J. Procter, *J. Am. Chem. Soc.* **2009**, *131*, 7214; c) M. Szostak, M. Spain, D. J. Procter, *Nat. Protoc.* **2012**, *7*, 970; d) M. Szostak, M. Spain, D. J. Procter, *Chem. Commun.* **2011**, *47*, 10254; e) M. Szostak, M. Spain, D. J. Procter, *Org. Lett.* **2012**, *14*, 840; f) M. Szostak, K. D. Collins, N. J. Fazakerley, M. Spain, D. J. Procter, *Org. Biomol. Chem.* **2012**, *10*, 5820; for a related study on TmI₂/H₂O, see: g) M. Szostak, M. Spain, D. J. Procter, *Angew. Chem.* **2013**, *125*, 7378; *Angew. Chem. Int. Ed.* **2013**, *52*, 7237.
- [14] a) P. R. Chopade, E. Prasad, R. A. Flowers II, *J. Am. Chem. Soc.* **2004**, *126*, 44; b) E. Prasad, R. A. Flowers II, *J. Am. Chem. Soc.* **2005**, *127*, 18093; c) M. Amiel-Levy, S. Hoz, *J. Am. Chem. Soc.* **2009**, *131*, 8280; d) E. Hasegawa, D. P. Curran, *J. Org. Chem.* **1993**, *58*, 5008.
- [15] a) A. Dahlén, G. Hilmersson, *Eur. J. Inorg. Chem.* **2004**, 3393; b) R. A. Flowers II, *Synlett* **2008**, 1427.
- [16] a) V. Malatesta, K. U. Ingold, *J. Am. Chem. Soc.* **1981**, *103*, 609; b) B. Giese, *Angew. Chem.* **1989**, *101*, 993; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969; c) T. Cohen, M. Bhupathy, *Acc. Chem. Res.* **1989**, *22*, 152.
- [17] A value of 1.5 is likely to result from a secondary KIE arising from differential coordination of D₂O/H₂O to Sm^{II}. For leading references on KIE, see: a) M. L. Bender, E. J. Pollock, M. C. Neveu, *J. Am. Chem. Soc.* **1962**, *84*, 595; b) "Theoretical and Experimental Aspects of Isotope Effects in Chemical Kinetics": J. Bigeleisen, M. Wolfsberg in *Advances in Chemical Physics*, Vol. 1 (Eds.: I. Prigogine, P. Debye), Wiley, Hoboken, **1958**; c) D. A. Singleton, A. A. Thomas, *J. Am. Chem. Soc.* **1995**, *117*, 9357; d) D. A. Singleton, M. J. Szymanski, *J. Am. Chem. Soc.* **1999**, *121*, 9455; e) J. G. Belasco, W. J. Albery, J. R. Knowles, *J. Am. Chem. Soc.* **1983**, *105*, 2475; f) M. H. O'Leary, *Annu. Rev. Biochem.* **1989**, *58*, 377. The absence of a primary KIE indicates that proton transfer is not involved in the rate-determining step of the reaction: g) K. B. Wiberg, *Chem. Rev.* **1955**, *55*, 713; h) M. Wolfsberg, *Acc. Chem. Res.* **1972**, *5*, 225; i) L. Melander, W. H. Saunders, *Reaction Rates of Isotopic Molecules*, Wiley, **1980**; j) E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.
- [18] R. W. Fessenden, R. H. Schuler, *J. Chem. Phys.* **1963**, *39*, 2147.
- [19] a) D. P. Curran, N. A. Porter, B. Giese, *Stereochemistry of Radical Reactions*, Wiley-VCH, Weinheim, **1996**; b) C. Chatgililoglu, A. Studer, *Encyclopedia of Radicals in Chemistry, Biology and Materials*, Wiley-Blackwell, Chichester, **2012**.
- [20] B. Giese, *Angew. Chem.* **1983**, *95*, 771; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753.
- [21] J. I. Bardagi, R. A. Rossi, *Org. Prep. Proced. Int.* **2009**, *41*, 479.
- [22] For a detailed study on the preparation of SmI₂: M. Szostak, M. Spain, D. J. Procter, *J. Org. Chem.* **2012**, *77*, 3049.
- [23] CCDC 948382 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.