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Mechanistic investigation of the selective reduction of Meldrum's acids to β-hydroxy acids using SmI_2 and H_2O†

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The mechanism of a recently reported first mono-reduction of cyclic 1,3-diesters (Meldrum's acids) to β-hydroxy acids with SmI_2–H_2O has been studied using a combination of reactivity, deuteration, kinetic isotope and radical clock experiments. Most crucially, the data indicate that the reaction proceeds *via* reversible electron transfer and that water, as a ligand for SmI_2, stabilizes the radical anion intermediate rather than only promoting the first electron transfer as originally proposed.

Reduction of carbonyl groups with low-valent metals to generate ketyl intermediates is a fundamental process in organic synthesis.[1] For more polar carboxylic acid derivatives, single electron transfer from the metal centre to form acyl-type radicals is more challenging due to lower electrophilicity of the carbonyl group precursors, which prevents selective electron transfer under mild conditions.[2] Moreover, the formed acyl-type radicals often undergo undesired decarbonylation to give carbon monoxide and alkyl radicals.[3] Accordingly, successful examples of generation of acyl-type radicals from polar carbonyl groups remain rare.[1–3]

Over the past decade, samarium(II) iodide (SmI_2, Kagan's reagent) has emerged as a valuable reagent for promoting electron transfer processes to carboxylic acid derivatives.[4,5] In particular, the reagent formed by activation of SmI_2 with Lewis basic ligands[6] has enabled mild and modular synthesis of acyl-type radical intermediates from various carboxylic acid precursors.[7,8] Perhaps most intriguing among these reagents are SmI_2–H_2O complexes[6b] formed *via* the addition of water to $SmI_2(THF)_n$ due to their excellent chemoselectivity in diverse radical reactions.[9]

Recently, our laboratory has demonstrated that SmI_2–H_2O exhibits remarkable selectivity in the reduction of carbonyl groups of cyclic 1,3-diesters (Fig. 1)[10] and lactones[11] in that the system shows full selectivity for the electron transfer to cyclic esters over their acyclic analogues. The reduction of cyclic 1,3-diesters (Meldrum's acids) with SmI_2[10] is of particular interest for the synthesis of β-hydroxy acids – important building blocks for the synthesis of pharmaceuticals and polymers[12] – directly from Meldrum's acids.[13] Furthermore, the easily assembled α,β-unsaturated Meldrum's acids[13] undergo sequential reductions in the presence of SmI_2–H_2O,[10a] providing a general route for the synthesis of β-hydroxy acids, while other methods involve multiple steps.[14] Finally, a large scale practical reduction of Meldrum's acids using SmI_2–H_2O has been developed,[10d,e] and the potential of acyl-type radical intermediates in cyclizations and reaction cascades has been demonstrated;[10b,c] however, at present the effect of the reaction components on the generation of acyl-type radicals from Meldrum's acids remains unclear.

Herein, we report the mechanistic investigation of the SmI_2–H_2O-promoted first mono-reduction of Meldrum's acids

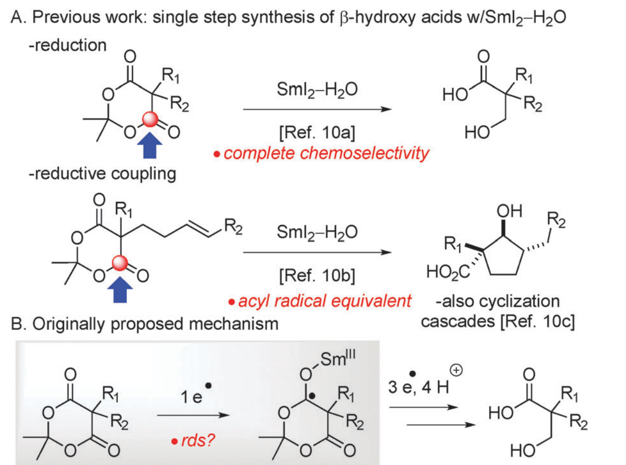

Fig. 1 (A) Previous studies: chemoselective electron transfer to Meldrum's acids (reduction, cyclization and cyclization cascades). (B) This work: mechanistic investigation and role of water.

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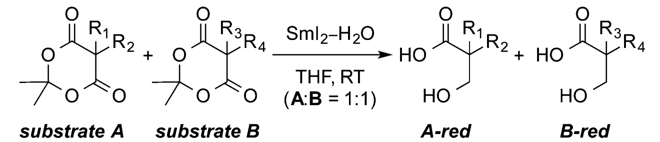
Table 1 Intermolecular competition experiments in the reduction of Meldrum's acids using SmI_2–H_2O[a]



Entry	A	B	R_1, R_2	R_3, R_4	k_A/k_B[b]
1	**1a**	**1b**	Ph, H	Bn, H	1.66
2	**1b**	**1c**	Bn, H	i-Bu, H	2.46
3	**1a**	**1c**	Ph, H	i-Bu, H	5.21
4	**1d**	**1a**	Ph, Me	Ph, H	> 20 : 1
5	**1e**	**1c**	i-Bu, Me	i-Bu, H	> 20 : 1
6	**1d**	**1e**	Ph, Me	i-Bu, Me	3.74
7[c,d]	**1f**	**1e**	=CHi-Pr	i-Bu, Me	> 20 : 1
8[c,d]	**1f**	**1d**	=CHi-Pr	Ph, Me	> 20 : 1
9[d]	**1h**	**1e**	–$(CH_2)_2$–	i-Bu, Me	> 20 : 1
10[d]	**1h**	**1d**	–$(CH_2)_2$–	Ph, Me	5.13
11[c,d]	**1f**	**1h**	=CHi-Pr	–$(CH_2)_2$–	> 20 : 1
12[c,d]	**1f**	**1g**	=CHi-Pr	=CHPh	1.37

[a] Conditions: Meldrum's acid (1 equiv.), SmI_2 (2 equiv., THF), H_2O (400 equiv.), 23 °C. Reaction time 30–60 s. [b] Determined by ^{1}H NMR. [c] SmI_2 (1 equiv.), H_2O (200 equiv.). In all entries > 95% yield based on reacted starting material. [d] Selective exo-cyclic reduction of olefin/cyclopropane to give the corresponding substituted Meldrum's acids. See ESI.

to β-hydroxy acids. The reaction proceeds *via* acyl-type radical intermediates generated by a direct electron transfer from Sm(II) to the ester carbonyl. The study represents one of the first mechanistic analyses of electron transfer processes to carbonyl groups mediated by SmI_2.[15] Importantly, this investigation outlines the interplay between SmI_2 and H_2O ligand,[16] establishes the reversibility of the initial electron transfer and provides insights for the rational development of radical reactions based on the versatile Meldrum's acid template using Sm(II) complexes.

Initial studies suggested that selectivity in the monoreduction of Meldrum's acids resulted from the rate of the initial electron transfer to the carbonyl group and anomeric stabilization of the radical anion intermediate.[10a,b] Moreover, water as the ligand to Sm(II) was critical for the observed reactivity. However, after continuous probing of the reaction pathway, several observations suggested that an alternative mechanism might be operative.

To elucidate the role of electronic and steric stabilization in the SmI_2-mediated reduction of Meldrum's acids, a series of reactivity studies were performed (Table 1).[17] Because of the heterogenicity of the reaction, kinetic studies proved not to be a viable tool in the present reaction. Remarkably, in the series of selected substrates (Table 1, entries 1–6) full selectivity for the reduction of alpha-disubstituted esters over alpha-monosubstituted esters was observed (Table 1, entries 4 and 5). Moreover, appreciable levels of selectivity were obtained depending on electronic properties of the α-carbon substituent at the ester group undergoing the reduction (Table 1, entries 1–3 and 6) consistent with electronic stabilization of ketyl-type radicals. The steric acceleration of the reduction is unexpected and contrasts with the previously observed steric inhibition of coordination of polar groups to Sm(II)

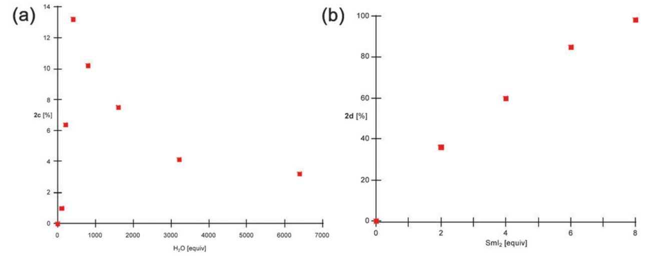


Fig. 2 (a) Plot of conversion *vs.* concentration of H_2O for reduction of **1c**. (b) Plot of conversion *vs.* concentration of SmI_2 for reduction of **1d**.

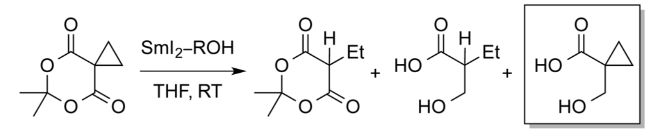
in the reduction of lactones and acyclic esters.[15a,b] We hypothesize that the steric acceleration in the present case results from a torsional strain in the radical anion intermediate in a half-chair conformation.[10a,b]

Evidence for the reaction pathway was further gained by examining the reactivity of substrates possessing two reactive sites (entries 7–12). These results indicate that α,β-unsaturated Meldrum's acids undergo chemoselective reduction in preference to their fully saturated counterparts (entries 7 and 8). Moreover, a cyclopropyl-clock containing substrate results in a faster reduction than for α,α-disubstituted Meldrum's acids (entries 9 and 10); however, its reduction is slower than that of an α,β-unsaturated ester (entry 11). Finally, electronically-differentiated α,β-unsaturated substrates result in a near statistical rate of reduction (entry 12). These results outline the order of reactivity of Meldrum's acids with SmI_2: α,β-unsaturated ≫ cyclopropyl > α,α-disubstituted ≫ α-monosubstituted.[18] Importantly, the data presented in Table 1 indicate high levels of chemoselectivity in the reduction of Meldrum's acids with SmI_2–H_2O.[5f]

To investigate the role of water as an activating ligand for Sm(II), a series of rate studies were performed (Fig. 2a and ESI†). Isobutyl-substituted ester was selected as a model substrate. The study was performed by monitoring the reduction of **1c** with increasing concentrations of water and quenching the reaction at low conversions. Remarkably, a non-linear dependence on water concentration was found in the reduction of **1c** (Fig. 2a). In agreement with the previous results, no reaction was observed without the water additive and at low concentration of water,[10a,b] (0–50 equiv.; see, ESI†). Next, at higher concentrations of water (100–400 equiv.) the rate was found to increase linearly with a slope. However, at high concentrations of water (> 400 equiv.) the rate decreased dramatically, which is consistent with substrate dissociation from the inner coordination sphere of Sm(II).[15] These results are in contrast to the thermodynamic redox potentials of SmI_2–H_2O complexes[15d] and other studies.[11b] Importantly, the rate of reduction of acyl-type radicals can be varied by simply changing the concentration of the water additive.[19]

We likewise investigated the role of SmI_2 in the reduction of Meldrum's acids (Fig. 2b and ESI†). The study was performed by monitoring the equivalents of SmI_2 required for the reduction of **1d** with a set concentration of water and quenching the reaction after disappearance of the active Sm(II)

Table 2 Radical clock fragmentation studies in the reduction of Meldrum's acids using SmI_2[a]



1h 2h 2i 2j, not detected

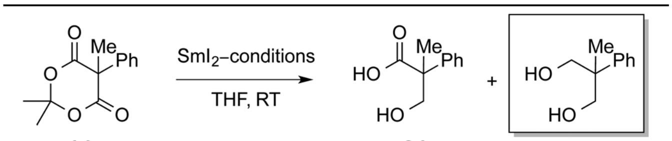
Entry	SmI_2 (equiv.)	ROH	ROH (equiv.)	Time	Conv.[b] (%)	2h : 2i[b] (%)
1	2	H_2O	200	<1 min	87	>95 : 5
2[c]	10	H_2O	1000	2 h	>95	<5 : >95
3[d]	3	MeOH	200	1 h	>95	>95 : 5
4[e]	3	—	—	3 h	50	>95 : 5

[a] Conditions: Meldrum's acid (1 equiv.), SmI_2 (in THF), ROH, 23 °C. [b] Determined by ^1H NMR. Combined yield of **2h** and **2i**. Entries 1–3, >85% yield based on reacted starting material. [c] Ref. 10*a*. [d] Fragmentation product consists of **2h** and its methanolysis product (15 : 85). [e] Entry 4, 23% yield. See ESI for full experimental details.

complex. As indicated in Fig. 2b, the reaction of **1d** is linear in SmI_2 and requires more than six equivalents of the reductant. This is consistent with previous mechanistic studies on the reduction of carbonyl groups with SmI_2[15] and indicates that the collapse of acetonide occurs prior to the final electron transfer from Sm(II).

To gain independent evidence on the role of electron transfer steps, we carried out experiments employing cyclopropyl clocks (Table 2 and ESI†).[20] The reaction of **1h** (2 equiv. of SmI_2) resulted in rapid cyclopropyl ring opening to give acyclic ester **2h**. Cyclopropyl carbinol was not detected in the reaction. The reaction with excess of SmI_2–H_2O (10 equiv., rt, 2 h)

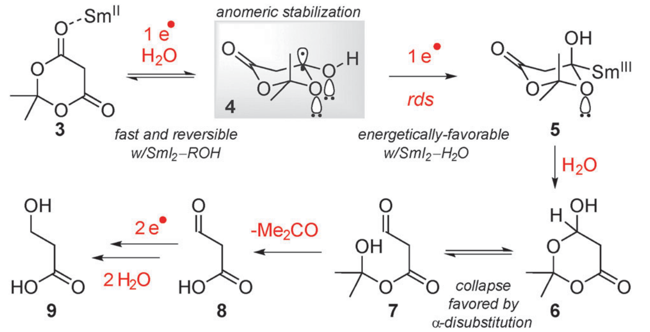
Table 3 Evaluation of chemoselectivity in the reduction of Meldrum's acids using SmI_2–ROH/L.B. systems[a]



1d 2d 2k, not detected

Entry	ROH/L.B.	ROH/L.B. (equiv.)	Time	Yield[b] (%)	Selectivity 2d : 2k[b] (%)
1	MeOH	4/1 v/v	2 h	<5	—
2	ED	36	2 h	<5	—
3	DCH	36	2 h	<5	—
4	EG	36	2 h	84	>95 : 5
5	*n*-$BuNH_2$/H_2O	12/18	5 min	<5	—
6	Pyrrolidine/H_2O	12/18	5 min	<5	—
7	Et_3N/H_2O	12/18	5 min	92	>95 : 5
8	Et_3N/EG	12/18	5 min	84	>95 : 5
9	Et_3N/MeOH	12/18	2 h	<5	—
10	TMEDA/H_2O	12/18	5 min	46	>95 : 5
11	*N*-Me-morpholine/H_2O	12/18	5 min	80	>95 : 5
12	DIPA/H_2O	12/18	5 min	48	>95 : 5

[a] Conditions: Meldrum's acid (1 equiv.), SmI_2 (4–6 equiv., THF), 23 °C. In all entries, preformed solution of SmI_2–ROH/L.B. was used. [b] Determined by ^1H NMR. In all entries, yield based on reacted starting material. ED = Ethylenediamine; DCH = *trans-N,N′*-dimethyl-1,2-cyclohexyldiamine; EG = ethylene glycol; TMEDA = tetramethylethylenediamine.



Scheme 1 Proposed mechanism of the reduction of Meldrum's acids.

resulted in a full reduction to the β-hydroxy acid. The reduction with SmI_2–H_2O (8 equiv., 15 min) gave approx. 1 : 1 ratio of **2h** to **2i**. The reduction using SmI_2–MeOH and SmI_2–THF resulted in alcoholysis and slow, non-selective reaction. Overall, these findings strongly suggest that the reduction of Meldrum's acids with SmI_2–H_2O occurs *via* fast, reversible electron transfer and that water activates the reagent towards the electron transfer.

Additional experiments were performed to gain insight into the electron transfer steps (see ESI† and Table 3). (1) The reduction of a series of α-mono and α,α-disubstituted substrates with SmI_2–D_2O gives the β-hydroxy acid products with >98% D^2 and D^3 incorporation, suggesting that anions are protonated in a series of electron transfer steps (see ESI†). Control reactions demonstrate that α-proton exchange is faster than the reduction (see ESI†). (2) The secondary kinetic isotope effect in the reduction of **1d** of 1.5 (intramolecular competition) suggests that proton transfer to carbon is not involved in the rate determining step of the reaction (see ESI†).[21] (3) The reduction of α,β-unsaturated Meldrum's acids **1f** and **1g** (SmI_2, 2 equiv.) proceeds with full selectivity for the 1,4-reduction to give saturated Meldrum's acid derivatives (see ESI†). (4) Evaluation of the reduction of the benchmark substrate using various Sm(II)–ROH systems indicates that other SmI_2 reagents can be used to promote selective mono-reduction (Table 3). Importantly, under the optimized reaction conditions over-reduction to 1,3-diol is not observed. Note, however, that the reactivity trend is divergent from the ligand effect on the reduction of other carbonyl groups using Sm(II),[15f] which most likely results from a combination of lower kinetic reactivity of these substrates (entries 1–4), instability towards the reaction conditions (entries 5 and 6), and differential coordination of the sterically-encumbered reductants to the Meldrum's acid carbonyl groups (entries 7–12). Overall, these results demonstrate that Sm(II) reagents based on chelating ligands[6] and multicomponent systems[7] are new chemoselective reductants available for the reduction of cyclic 1,3-diesters.

Scheme 1 shows a revised mechanism that is consistent with the kinetic and reactivity studies presented herein. The key features involve: (1) reversible initial electron transfer step; (2) non-linear rate dependence on water concentration; (3) rate determining second electron transfer step that is inhibited by large concentrations of water.

In conclusion, we have elucidated the mechanism of the selective mono-reduction of Meldrum's acids to β-hydroxy acids using the SmI_2–H_2O system. We hope that further research aimed at understanding processes involving activation of SmI_2 by Lewis basic ligands will enable discovery of new radical reactions.

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Notes and references

1 Reviews on metal-mediated radical reactions: (*a*) B. M. Trost and I. Fleming, *Comprehensive Organic Synthesis*, Pergamon Press, 1991; (*b*) A. Gansäuer and H. Bluhm, *Chem. Rev.*, 2000, **100**, 2771; (*c*) M. Szostak and D. J. Procter, *Angew. Chem., Int. Ed.*, 2012, **51**, 9238; (*d*) J. Streuff, *Synthesis*, 2013, **45**, 281.

2 For reviews see: (*a*) P. Renaud and M. Sibi, *Radicals in Organic Synthesis*, Wiley-VCH, 2001; (*b*) C. Chatgilialoglu and A. Studer, *Encyclopedia of Radicals in Chemistry*, Biology and Materials, Wiley-Blackwell, 2012; (*c*) T. Wirth, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 61; (*d*) J. Murphy, *J. Org. Chem.*, 2014, **79**, 3731.

3 For a comprehensive review, see: (*a*) C. Chatgilialoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **99**, 1991; For an elegant solution using SmI_2, see: (*b*) C. M. Jensen, K. B. Lindsay, R. H. Taaning, J. Karaffa, A. M. Hansen and T. Skrydstrup, *J. Am. Chem. Soc.*, 2005, **127**, 6544.

4 D. J. Procter, R. A. Flowers, II and T. Skrydstrup, *Organic Synthesis using Samarium Diiodide: A Practical Guide*, RSC Publishing, Cambridge, 2009.

5 Recent reviews on SmI_2: (*a*) H. B. Kagan, *Tetrahedron*, 2003, **59**, 10351; (*b*) D. J. Edmonds, D. Johnston and D. J. Procter, *Chem. Rev.*, 2004, **104**, 3371; (*c*) K. C. Nicolaou, S. P. Ellery and J. S. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 7140; (*d*) C. Beemelmanns and H. U. Reissig, *Chem. Soc. Rev.*, 2011, **40**, 2199; (*e*) M. Szostak and D. J. Procter, *Angew. Chem., Int. Ed.*, 2011, **50**, 7737; (*f*) M. Szostak, M. Spain and D. J. Procter, *Chem. Soc. Rev.*, 2013, **42**, 9155; (*g*) M. Szostak, N. J. Fazakerley, D. Parmar and D. J. Procter, *Chem. Rev.*, 2014, **114**, DOI: 10.1021/cr400685r.

6 For reviews on the influence of additives on properties of SmI_2, see: (*a*) A. Dahlén and G. Hilmersson, *Eur. J. Inorg. Chem.*, 2004, 3393; (*b*) M. Szostak, M. Spain, D. Parmar and D. J. Procter, *Chem. Commun.*, 2012, **48**, 330.

7 For early studies, see: (*a*) Y. Kamochi and T. Kudo, *Chem. Lett.*, 1993, 1495; (*b*) Y. Kamochi and T. Kudo, *Tetrahedron*, 1992, **48**, 4301; Recent examples: (*c*) M. Szostak, M. Spain and D. J. Procter, *Chem. Commun.*, 2011, **47**, 10254; (*d*) M. Szostak, M. Spain and D. J. Procter, *Org. Lett.*, 2012, **14**, 840; (*e*) M. Szostak, K. D. Collins, N. J. Fazakerley, M. Spain and D. J. Procter, *Org. Biomol. Chem.*, 2012, **10**, 5820; (*f*) M. Szostak, M. Spain, A. J. Eberhart and D. J. Procter, *J. Am. Chem. Soc.*, 2014, **136**, 2268; (*g*) M. Szostak, B. Sautier, M. Spain and D. J. Procter, *Org. Lett.*, 2014, **16**, 1092.

8 Representative examples of Sm(II)-Lewis base systems in other transformations: (*a*) A. Dahlén and G. Hilmersson, *Tetrahedron Lett.*, 2002, **43**, 7197; (*b*) A. Dahlén and G. Hilmersson, *J. Am. Chem. Soc.*, 2005, **127**, 8340; (*c*) C. Beemelmanns and H. U. Reissig, *Angew. Chem., Int. Ed.*, 2010, **49**, 8021; (*d*) Z. Li, M. Nakashige and W. J. Chain, *J. Am. Chem. Soc.*, 2011, **133**, 6553.

9 Representative examples of SmI_2–H_2O systems: (*a*) E. Hasegawa and D. P. Curran, *J. Org. Chem.*, 1993, **58**, 5008; (*b*) G. Masson, P. Cividino, S. Py and Y. Vallée, *Angew. Chem., Int. Ed.*, 2003, **42**, 2265; (*c*) P. Gilles and S. Py, *Org. Lett.*, 2012, **14**, 1042.

10 (*a*) G. Guazzelli, S. De Grazia, K. D. Collins, H. Matsubara, M. Spain and D. J. Procter, *J. Am. Chem. Soc.*, 2009, **131**, 7214; (*b*) 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; (*c*) B. Sautier, S. E. Lyons, M. R. Webb and D. J. Procter, *Org. Lett.*, 2012, **14**, 146; (*d*) M. Szostak, M. Spain and D. J. Procter, *Nat. Protoc.*, 2012, **7**, 970; Detailed study on the preparation of SmI_2: (*e*) M. Szostak, M. Spain and D. J. Procter, *J. Org. Chem.*, 2012, **77**, 3049; (*f*) M. Szostak, B. Sautier, M. Spain, M. Behlendorf and D. J. Procter, *Angew. Chem., Int. Ed.*, 2013, **52**, 12559.

11 (*a*) L. A. Duffy, H. Matsubara and D. J. Procter, *J. Am. Chem. Soc.*, 2008, **130**, 1136; (*b*) D. Parmar, L. A. Duffy, D. V. Sadasivam, H. Matsubara, P. A. Bradley, R. A. Flowers, II and D. J. Procter, *J. Am. Chem. Soc.*, 2009, **131**, 15467; (*c*) D. Parmar, K. Price, M. Spain, H. Matsubara, P. A. Bradley and D. J. Procter, *J. Am. Chem. Soc.*, 2011, **133**, 2418; (*d*) D. Parmar, H. Matsubara, K. Price, M. Spain and D. J. Procter, *J. Am. Chem. Soc.*, 2012, **134**, 12751; (*e*) M. Szostak, M. Spain, K. A. Choquette, R. A. Flowers, II and D. J. Procter, *J. Am. Chem. Soc.*, 2013, **135**, 15702; Application to TmI_2–H_2O: (*f*) M. Szostak, M. Spain and D. J. Procter, *Angew. Chem., Int. Ed.*, 2013, **52**, 7237. Application to Birch reductions: (*g*) M. Szostak, M. Spain and D. J. Procter, *J. Org. Chem.*, 2014, **79**, 2522.

12 Representative examples: (*a*) B. Hu, M. Prashad, D. Har, K. Prasad, O. Repič and T. J. Blacklock, *Org. Process Res. Dev.*, 2007, **11**, 90; (*b*) H. S. Lee and D. H. Kim, *Bioorg. Med. Chem.*, 2003, **11**, 4685; (*c*) P. M. Chaudhari, P. V. Kawade and S. M. Funne, *Int. J. Pharm. Technol.*, 2011, **3**, 774; (*d*) D. Zhang, M. A. Hillmyer and W. B. Tolman, *Macromolecules*, 2004, **37**, 8198.

13 Comprehensive reviews on Meldrum's acids: (*a*) H. McNab, *Chem. Soc. Rev.*, 1978, **7**, 345; (*b*) B. C. Chen, *Heterocycles*, 1991, **32**, 529; (*c*) A. M. Dumas and E. Fillion, *Acc. Chem. Res.*, 2010, **43**, 440.

14 M. O. Polla, L. Tottie, C. Nordén, M. Linschoten, D. Müsila, S. Trumpp-Kallmeyer, I. R. Aukrust, R. Ringom, K. H. Holm, S. M. Neset, M. Sandberg, J. Thurmond, P. Yu, G. Hategan and H. Anderson, *Bioorg. Med. Chem.*, 2004, **12**, 1151.

15 Relevant studies on mechanisms of SmI_2-mediated reactions: (*a*) M. Szostak, M. Spain and D. J. Procter, *Chem. – Eur. J.*, 2014, **20**, 4222; (*b*) M. Szostak, M. Spain and D. J. Procter, *J. Am. Chem. Soc.*, 2014, **136**, DOI: 10.1021/ja503494b; (*c*) T. Ankner and G. Hilmersson, *Tetrahedron*, 2009, **65**, 10856; (*d*) P. R. Chopade, E. Prasad and R. A. Flowers, II, *J. Am. Chem. Soc.*, 2004, **126**, 44; (*e*) E. Prasad and R. A. Flowers, II, *J. Am. Chem. Soc.*, 2005, **127**, 18093; (*f*) D. V. Sadasivam, J. A. Teprovich, Jr., D. J. Procter and R. A. Flowers, II, *Org. Lett.*, 2010, **12**, 4140.

16 (*a*) A. Yacovan, I. Bilkis and S. Hoz, *J. Am. Chem. Soc.*, 1996, **118**, 261; (*b*) A. Tarnopolsky and S. Hoz, *J. Am. Chem. Soc.*, 2007, **129**, 3402; (*c*) M. Amiel-Levy and S. Hoz, *J. Am. Chem. Soc.*, 2009, **131**, 8280; (*d*) S. K. Upadhyay and S. Hoz, *J. Org. Chem.*, 2011, **76**, 1355.

17 R. H. Taaning, K. B. Lindsay, B. Schiøtt, K. Daasbjerg and T. Skrydstrup, *J. Am. Chem. Soc.*, 2009, **131**, 10253.

18 Relative reactivity of Meldrum's acids with SmI_2–H_2O: Meldrum's acids ≫ barbituric acids ≫ lactones. See, ref. 10*f*.

19 The onset of reactivity and maximum rate of the reduction of Meldrum's acids is shifted towards higher concentrations of water than the reduction of lactones using SmI_2–H_2O, despite the rate of lactone reduction being slower than the rate of Meldrum's acid reduction.[18] See, also: H. Farran and S. Hoz, *Org. Lett.*, 2008, **10**, 4875.

20 M. Newcomb, *Tetrahedron*, 1993, **49**, 1151.

21 E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066.