

# Mechanistic investigation of the selective reduction of Meldrum's acids to $\beta$ -hydroxy acids using $\text{SmI}_2$ and $\text{H}_2\text{O}$ †

Michal Szostak,\* Sarah E. Lyons, Malcolm Spain and David J. Procter\*

Cite this: *Chem. Commun.*, 2014, 50, 8391Received 30th April 2014,  
Accepted 5th June 2014

DOI: 10.1039/c4cc03216k

www.rsc.org/chemcomm

The mechanism of a recently reported first mono-reduction of cyclic 1,3-diester (Meldrum's acids) to  $\beta$ -hydroxy acids with  $\text{SmI}_2\text{-H}_2\text{O}$  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  $\text{SmI}_2$ , 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.<sup>1</sup> 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.<sup>2</sup> Moreover, the formed acyl-type radicals often undergo undesired decarbonylation to give carbon monoxide and alkyl radicals.<sup>3</sup> Accordingly, successful examples of generation of acyl-type radicals from polar carbonyl groups remain rare.<sup>1–3</sup>

Over the past decade, samarium(II) iodide ( $\text{SmI}_2$ , Kagan's reagent) has emerged as a valuable reagent for promoting electron transfer processes to carboxylic acid derivatives.<sup>4,5</sup> In particular, the reagent formed by activation of  $\text{SmI}_2$  with Lewis basic ligands<sup>6</sup> has enabled mild and modular synthesis of acyl-type radical intermediates from various carboxylic acid precursors.<sup>7,8</sup> Perhaps most intriguing among these reagents are  $\text{SmI}_2\text{-H}_2\text{O}$  complexes<sup>6b</sup> formed via the addition of water to  $\text{SmI}_2(\text{THF})_n$  due to their excellent chemoselectivity in diverse radical reactions.<sup>9</sup>

Recently, our laboratory has demonstrated that  $\text{SmI}_2\text{-H}_2\text{O}$  exhibits remarkable selectivity in the reduction of carbonyl

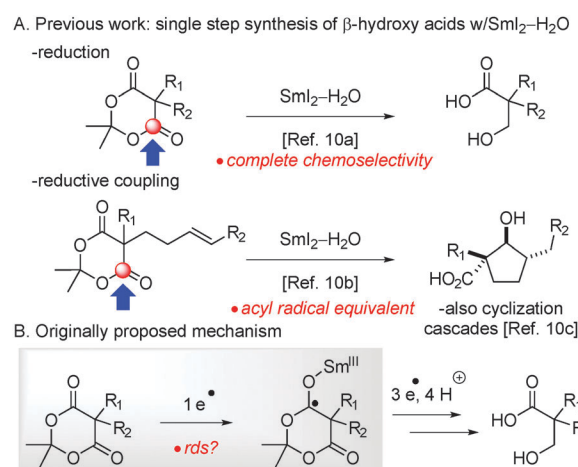


Fig. 1 (A) Previous studies: chemoselective electron transfer to Meldrum's acids (reduction, cyclization and cyclization cascades). (B) This work: mechanistic investigation and role of water.

groups of cyclic 1,3-diester (Fig. 1)<sup>10</sup> and lactones<sup>11</sup> in that the system shows full selectivity for the electron transfer to cyclic esters over their acyclic analogues. The reduction of cyclic 1,3-diester (Meldrum's acids) with  $\text{SmI}_2$ <sup>10</sup> is of particular interest for the synthesis of  $\beta$ -hydroxy acids – important building blocks for the synthesis of pharmaceuticals and polymers<sup>12</sup> – directly from Meldrum's acids.<sup>13</sup> Furthermore, the easily assembled  $\alpha,\beta$ -unsaturated Meldrum's acids<sup>13</sup> undergo sequential reductions in the presence of  $\text{SmI}_2\text{-H}_2\text{O}$ ,<sup>10a</sup> providing a general route for the synthesis of  $\beta$ -hydroxy acids, while other methods involve multiple steps.<sup>14</sup> Finally, a large scale practical reduction of Meldrum's acids using  $\text{SmI}_2\text{-H}_2\text{O}$  has been developed,<sup>10d,e</sup> and the potential of acyl-type radical intermediates in cyclizations and reaction cascades has been demonstrated,<sup>10b,c</sup> 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  $\text{SmI}_2\text{-H}_2\text{O}$ -promoted first mono-reduction of Meldrum's acids

School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK. E-mail: michal.szostak@manchester.ac.uk, david.j.procter@manchester.ac.uk; Fax: +44 (0)161 2754939; Tel: +44 (0)161 2751425

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc03216k



**Table 1** Intermolecular competition experiments in the reduction of Meldrum's acids using  $\text{SmI}_2\text{-H}_2\text{O}^a$ 

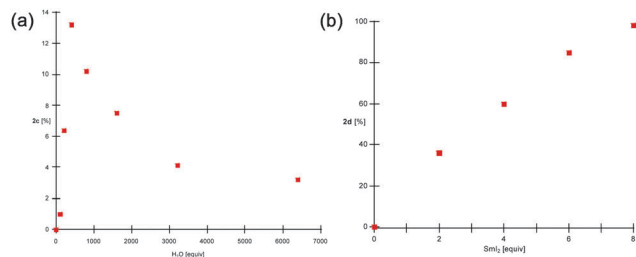
Entry	substrate		$\text{R}_1, \text{R}_2$		$\text{R}_3, \text{R}_4$		$k_A/k_B^b$
	A	B	A-red	B-red	A-red	B-red	
1	<b>1a</b>	<b>1b</b>	Ph, H	Bn, H	1.66		
2	<b>1b</b>	<b>1c</b>	Bn, H	i-Bu, H	2.46		
3	<b>1a</b>	<b>1c</b>	Ph, H	i-Bu, H	5.21		
4	<b>1d</b>	<b>1a</b>	Ph, Me	Ph, H	> 20 : 1		
5	<b>1e</b>	<b>1c</b>	i-Bu, Me	i-Bu, H	> 20 : 1		
6	<b>1d</b>	<b>1e</b>	Ph, Me	i-Bu, Me	3.74		
7 <sup>c,d</sup>	<b>1f</b>	<b>1e</b>	=Chi-Pr	i-Bu, Me	> 20 : 1		
8 <sup>c,d</sup>	<b>1f</b>	<b>1d</b>	=Chi-Pr	Ph, Me	> 20 : 1		
9 <sup>d</sup>	<b>1h</b>	<b>1e</b>	-(CH <sub>2</sub> ) <sub>2</sub> -	i-Bu, Me	> 20 : 1		
10 <sup>d</sup>	<b>1h</b>	<b>1d</b>	-(CH <sub>2</sub> ) <sub>2</sub> -	Ph, Me	5.13		
11 <sup>c,d</sup>	<b>1f</b>	<b>1h</b>	=Chi-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -	> 20 : 1		
12 <sup>c,d</sup>	<b>1f</b>	<b>1g</b>	=Chi-Pr	=CHPh	1.37		

<sup>a</sup> Conditions: Meldrum's acid (1 equiv.),  $\text{SmI}_2$  (2 equiv., THF),  $\text{H}_2\text{O}$  (400 equiv.), 23 °C. Reaction time 30–60 s. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup>  $\text{SmI}_2$  (1 equiv.),  $\text{H}_2\text{O}$  (200 equiv.). In all entries > 95% yield based on reacted starting material. <sup>d</sup> Selective exo-cyclic reduction of olefin/cyclopropane to give the corresponding substituted Meldrum's acids. See ESI.

to  $\beta$ -hydroxy acids. The reaction proceeds *via* acyl-type radical intermediates generated by a direct electron transfer from  $\text{Sm}(\text{II})$  to the ester carbonyl. The study represents one of the first mechanistic analyses of electron transfer processes to carbonyl groups mediated by  $\text{SmI}_2$ .<sup>15</sup> Importantly, this investigation outlines the interplay between  $\text{SmI}_2$  and  $\text{H}_2\text{O}$  ligand,<sup>16</sup> 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  $\text{Sm}(\text{II})$  complexes.

Initial studies suggested that selectivity in the mono-reduction 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.<sup>10a,b</sup> Moreover, water as the ligand to  $\text{Sm}(\text{II})$  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  $\text{SmI}_2$ -mediated reduction of Meldrum's acids, a series of reactivity studies were performed (Table 1).<sup>17</sup> Because of the heterogeneity 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  $\alpha$ -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  $\text{Sm}(\text{II})$

**Fig. 2** (a) Plot of conversion vs. concentration of  $\text{H}_2\text{O}$  for reduction of **1c**. (b) Plot of conversion vs. concentration of  $\text{SmI}_2$  for reduction of **1d**.

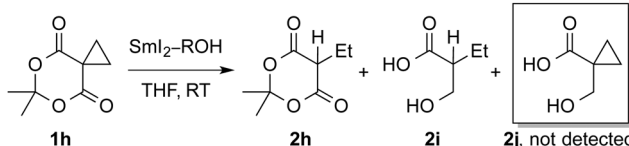
in the reduction of lactones and acyclic esters.<sup>15a,b</sup> We hypothesize that the steric acceleration in the present case results from a torsional strain in the radical anion intermediate in a half-chair conformation.<sup>10a,b</sup>

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  $\alpha,\beta$ -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  $\alpha,\alpha$ -disubstituted Meldrum's acids (entries 9 and 10); however, its reduction is slower than that of an  $\alpha,\beta$ -unsaturated ester (entry 11). Finally, electronically-differentiated  $\alpha,\beta$ -unsaturated substrates result in a near statistical rate of reduction (entry 12). These results outline the order of reactivity of Meldrum's acids with  $\text{SmI}_2$ :  $\alpha,\beta$ -unsaturated  $\gg$  cyclopropyl  $>$   $\alpha,\alpha$ -disubstituted  $\gg$   $\alpha$ -monosubstituted.<sup>18</sup> Importantly, the data presented in Table 1 indicate high levels of chemoselectivity in the reduction of Meldrum's acids with  $\text{SmI}_2\text{-H}_2\text{O}$ .<sup>5f</sup>

To investigate the role of water as an activating ligand for  $\text{Sm}(\text{II})$ , 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,<sup>10a,b</sup> (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  $\text{Sm}(\text{II})$ .<sup>15</sup> These results are in contrast to the thermodynamic redox potentials of  $\text{SmI}_2\text{-H}_2\text{O}$  complexes<sup>15d</sup> and other studies.<sup>11b</sup> Importantly, the rate of reduction of acyl-type radicals can be varied by simply changing the concentration of the water additive.<sup>19</sup>

We likewise investigated the role of  $\text{SmI}_2$  in the reduction of Meldrum's acids (Fig. 2b and ESI†). The study was performed by monitoring the equivalents of  $\text{SmI}_2$  required for the reduction of **1d** with a set concentration of water and quenching the reaction after disappearance of the active  $\text{Sm}(\text{II})$



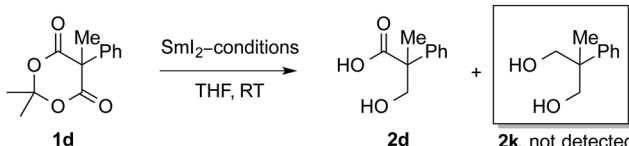
**Table 2** Radical clock fragmentation studies in the reduction of Meldrum's acids using  $\text{SmI}_2^a$ 


Entry	$\text{SmI}_2$ (equiv.)	ROH	ROH (equiv.)	Time	Conv. <sup>b</sup> (%)	<b>2h</b> : <b>2i</b> <sup>b</sup> (%)
1	2	$\text{H}_2\text{O}$	200	<1 min	87	>95:5
2 <sup>c</sup>	10	$\text{H}_2\text{O}$	1000	2 h	>95	<5:>95
3 <sup>d</sup>	3	MeOH	200	1 h	>95	>95:5
4 <sup>e</sup>	3	—	—	3 h	50	>95:5

<sup>a</sup> Conditions: Meldrum's acid (1 equiv.),  $\text{SmI}_2$  (in THF), ROH, 23 °C. <sup>b</sup> Determined by  $^1\text{H}$  NMR. Combined yield of **2h** and **2i**. Entries 1–3, >85% yield based on reacted starting material. <sup>c</sup> Ref. 10a. <sup>d</sup> Fragmentation product consists of **2h** and its methanolysis product (15:85). <sup>e</sup> Entry 4, 23% yield. See ESI for full experimental details.

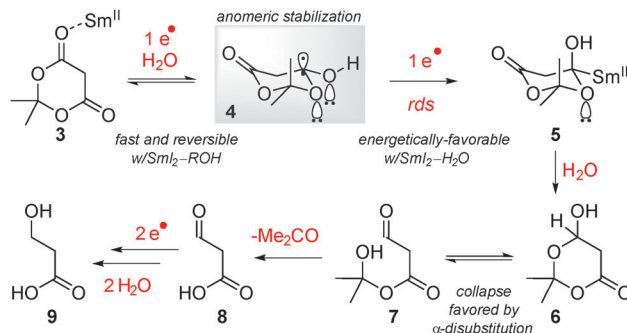
complex. As indicated in Fig. 2b, the reaction of **1d** is linear in  $\text{SmI}_2$  and requires more than six equivalents of the reductant. This is consistent with previous mechanistic studies on the reduction of carbonyl groups with  $\text{SmI}_2^{15}$  and indicates that the collapse of acetonide occurs prior to the final electron transfer from  $\text{Sm}(\text{II})$ .

To gain independent evidence on the role of electron transfer steps, we carried out experiments employing cyclopropyl clocks (Table 2 and ESI†).<sup>20</sup> The reaction of **1h** (2 equiv. of  $\text{SmI}_2$ ) resulted in rapid cyclopropyl ring opening to give acyclic ester **2h**. Cyclopropyl carbinol was not detected in the reaction. The reaction with excess of  $\text{SmI}_2\text{-H}_2\text{O}$  (10 equiv., rt, 2 h)

**Table 3** Evaluation of chemoselectivity in the reduction of Meldrum's acids using  $\text{SmI}_2\text{-ROH/L.B.}$  systems<sup>a</sup>


Entry	ROH/L.B.	ROH/L.B. (equiv.)	Time	Yield <sup>b</sup> (%)	Selectivity <b>2d</b> : <b>2k</b> <sup>b</sup> (%)
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	<i>n</i> -BuNH <sub>2</sub> /H <sub>2</sub> O	12/18	5 min	<5	—
6	Pyrrolidine/H <sub>2</sub> O	12/18	5 min	<5	—
7	Et <sub>3</sub> N/H <sub>2</sub> O	12/18	5 min	92	>95:5
8	Et <sub>3</sub> N/EG	12/18	5 min	84	>95:5
9	Et <sub>3</sub> N/MeOH	12/18	2 h	<5	—
10	TMEDA/H <sub>2</sub> O	12/18	5 min	46	>95:5
11	<i>N</i> -Me-morpholine/H <sub>2</sub> O	12/18	5 min	80	>95:5
12	DIPA/H <sub>2</sub> O	12/18	5 min	48	>95:5

<sup>a</sup> Conditions: Meldrum's acid (1 equiv.),  $\text{SmI}_2$  (4–6 equiv., THF), 23 °C. In all entries, preformed solution of  $\text{SmI}_2\text{-ROH/L.B.}$  was used. <sup>b</sup> Determined by  $^1\text{H}$  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  $\beta$ -hydroxy acid. The reduction with  $\text{SmI}_2\text{-H}_2\text{O}$  (8 equiv., 15 min) gave approx. 1:1 ratio of **2h** to **2i**. The reduction using  $\text{SmI}_2\text{-MeOH}$  and  $\text{SmI}_2\text{-THF}$  resulted in alcoholysis and slow, non-selective reaction. Overall, these findings strongly suggest that the reduction of Meldrum's acids with  $\text{SmI}_2\text{-H}_2\text{O}$  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  $\alpha$ -mono and  $\alpha,\alpha$ -disubstituted substrates with  $\text{SmI}_2\text{-D}_2\text{O}$  gives the  $\beta$ -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  $\alpha$ -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†).<sup>21</sup> (3) The reduction of  $\alpha,\beta$ -unsaturated Meldrum's acids **1f** and **1g** ( $\text{SmI}_2$ , 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  $\text{Sm}(\text{II})\text{-ROH}$  systems indicates that other  $\text{SmI}_2$  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  $\text{Sm}(\text{II})$ ,<sup>15f</sup> 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  $\text{Sm}(\text{II})$  reagents based on chelating ligands<sup>6</sup> and multicomponent systems<sup>7</sup> 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  $\beta$ -hydroxy acids



using the  $\text{SmI}_2\text{-H}_2\text{O}$  system. We hope that further research aimed at understanding processes involving activation of  $\text{SmI}_2$  by Lewis basic ligands will enable discovery of new radical reactions.

We are grateful to the EPSRC and GSK for financial support.

## Notes and references

- 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.
- For reviews see: (a) P. Renaud and M. Sibi, *Radicals in Organic Synthesis*, Wiley-VCH, 2001; (b) C. Chatgililoglu 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.
- For a comprehensive review, see: (a) C. Chatgililoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **99**, 1991; For an elegant solution using  $\text{SmI}_2$ , 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.
- D. J. Procter, R. A. Flowers, II and T. Skrydstrup, *Organic Synthesis using Samarium Diodide: A Practical Guide*, RSC Publishing, Cambridge, 2009.
- Recent reviews on  $\text{SmI}_2$ : (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. Beemelmans 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.
- For reviews on the influence of additives on properties of  $\text{SmI}_2$ , 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.
- 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.
- Representative examples of  $\text{Sm(II)}$ -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. Beemelmans 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.
- Representative examples of  $\text{SmI}_2\text{-H}_2\text{O}$  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.
- (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  $\text{SmI}_2$ : (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.
- (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  $\text{TmI}_2\text{-H}_2\text{O}$ : (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.
- Representative examples: (a) B. Hu, M. Prasad, 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.
- 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.
- M. O. Polla, L. Tottie, C. Nordén, M. Linschoten, D. Mülisa, 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.
- Relevant studies on mechanisms of  $\text{SmI}_2$ -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.
- (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.
- R. H. Taaning, K. B. Lindsay, B. Schiött, K. Daasbjerg and T. Skrydstrup, *J. Am. Chem. Soc.*, 2009, **131**, 10253.
- Relative reactivity of Meldrum's acids with  $\text{SmI}_2\text{-H}_2\text{O}$ : Meldrum's acids  $\gg$  barbituric acids  $\gg$  lactones. See, ref. 10f.
- 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  $\text{SmI}_2\text{-H}_2\text{O}$ , despite the rate of lactone reduction being slower than the rate of Meldrum's acid reduction.<sup>18</sup> See, also: H. Farran and S. Hoz, *Org. Lett.*, 2008, **10**, 4875.
- M. Newcomb, *Tetrahedron*, 1993, **49**, 1151.
- E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066.

