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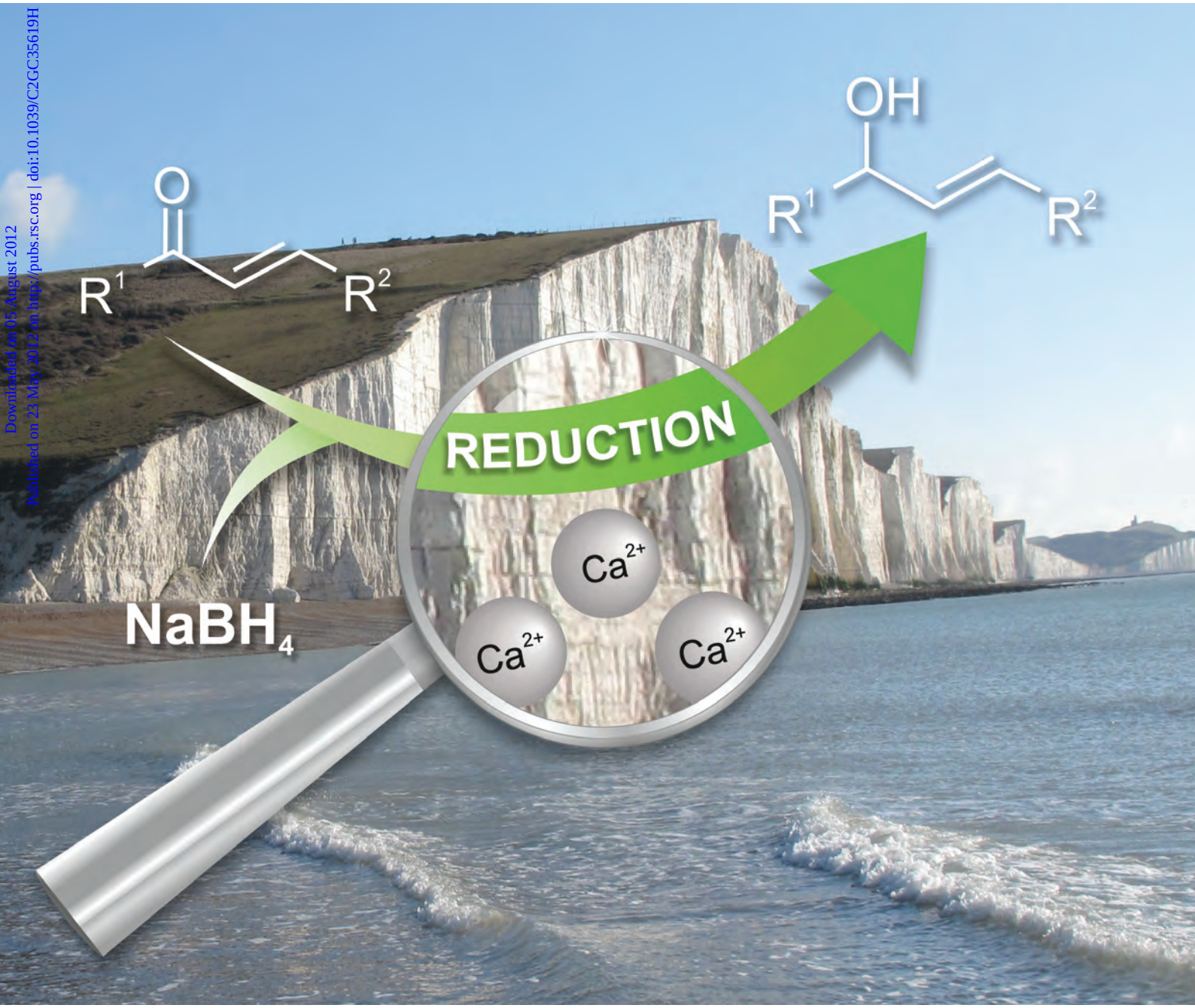

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COMMUNICATION

Lanthanide replacement in organic synthesis: Luche-type reduction of α,β-unsaturated ketones in the presence of calcium triflate†

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Development of a calcium-mediated regioselective 1,2-reduction of challenging α,β-unsaturated ketones, such as 2-cyclopententone, is reported. The corresponding allylic alcohols are obtained in very good regioselectivities using $Ca(OTf)_2$ and $NaBH_4$. Furthermore, we have shown that our method can stereoselectively reduce aziridinyl ketones.

Introduction

The privileged position of trivalent lanthanide salts (along with the chemically similar rare earth elements Sc and Y) in selective organic synthesis is secured due to their applicability to a number of processes, including oxidation, reduction and C–C bond forming reactions.[1] Despite this, there are several drawbacks to their wider use, particularly in the synthesis of pharmaceuticals, which likely limits their use in pharmaceutical industry. In the first instance, many of the lanthanide and other rare earth elements are prohibitively expensive, especially for large-scale and stoichiometric reactions. Also, while generally the lanthanide salts are considered non-toxic, this is primarily due to their inability to cross cell membranes, and they are therefore not absorbed if orally ingested. If administered intravenously however, they are significantly toxic, gaining access to intracellular calcium channels.[2] Lack of information regarding the Life Cycle Analysis of these reagents makes comparison to conventional alternatives in the chemical industries difficult. It is likely however, that their main limitations stem from the lack of industrial experience in their utilisation, combined with their reduced availability and increased purchase and cost. In addition, since they contain rare metals, the production of these reagents may itself be a polluting or hazardous process.

The alkaline earth metals Mg, Ca, Sr and Ba are widely abundant, cheap and largely environmentally benign. It is well established that the reactivity and coordination behaviour of the heavier alkaline earth metals, especially Ca, is somewhat similar to the lanthanide metals.[3] This fact is slowly beginning to be appreciated in the field of organic synthesis.[4] Elegant studies by Hill, Barrett and co-workers have demonstrated bulky calcium amides as catalysts for hydroamination[5] and hydrophosphination of olefins,[6] as well as in the Tischenko reaction.[7] Blechert and co-workers have also studied related calcium catalysts in hydroamination chemistry.[8] Harder and co-workers have demonstrated calcium catalysis in hydroboration, hydrosilylation, and hydrogenation reactions.[9] There have also been reports on calcium-catalysed Friedel–Crafts alkylation and hydroarylation,[10] as well as the use of efficient chiral calcium complexes for asymmetric reactions.[11]

The selective reduction of α,β-unsaturated carbonyls with sodium borohydride in the presence of cerium(III) chloride in methanol, known as the Luche reduction, is a common and simple method to synthesise allylic alcohols.[12] We decided to investigate whether calcium salts would be a suitable replacement for cerium(III) chloride in this selective reduction. While many of the calcium-mediated processes highlighted above rely on calcium complexes that are highly air and moisture sensitive, we selected to use only salts bearing hard conjugate bases, such as $^{-}$OTf, to afford water-stable complexes, a function of the p*K*a value of the ligand.[13] A preliminary report on the use of calcium chloride in this chemistry appeared in 1991.[14] However, the selectivity of 1,2-reduction *versus* the competing 1,4-reduction was limited, especially for challenging substrates such as 2-cyclopentenone **1**, which is known to undergo 1,4-reduction more readily than 1,2-reduction. We envisaged that suitable tuning of the calcium salt employed and the reaction conditions should give access to a calcium-based protocol which rivals the classical Luche process.

Results and discussion

Our initial studies began with the optimisation of the reaction conditions for the model reaction shown in Table 1. We found that with stoichiometric amounts of sodium borohydride and calcium chloride in MeOH at rt, reduction of enone **1** afforded unsaturated alcohol **2** and saturated alcohol **3** as an approximately 50 : 50 mixture (entry 1, Table 1), while no calcium additive gave total selectivity for saturated alcohol **3** (entry 3, Table 1, for complete initial screen table see ESI†). Encouraged by this, we performed a full reaction parameter screen for calcium chloride varying the reaction conditions. Key to our

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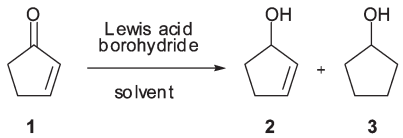
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2gc35619h

Table 1 Reaction parameter screen with 2-cyclopentenone as model substrate[a]

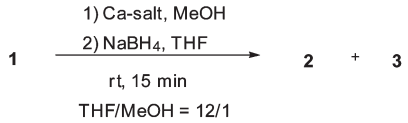


1 2 3

Entry	Lewis acid	Conditions	Selectivity[b] 2	3
1[b]	$CaCl_2$	$NaBH_4$, rt, MeOH	48	52
2	$CeCl_3{\cdot}7H_2O$	$NaBH_4$, rt, MeOH	97	3
3	—	$NaBH_4$, rt, MeOH	0	100
4	$CaCl_2$	$NaBH_4$, rt, EtOH	40	60
5	$CaCl_2$	$NaBH_4$, rt, iPrOH	26	74
6	$CaCl_2$	$NaBH_4$, rt, THF	27	73
7	$CaCl_2$	$NaBH_4$, rt, H_2O	15	85
8	$CaCl_2$	$NaBH_4$, 0 °C, MeOH	25	75
9	$CaCl_2$	$LiBH_4$, rt, MeOH	35	65
10	$CeCl_3{\cdot}7H_2O$	$LiBH_4$, rt, MeOH	100	0
11	—	$LiBH_4$, rt, MeOH	0	100
12	$CaCl_2$	NBu_4BH_4, rt, MeOH	39	61
13	$CaCl_2$	$Ca(BH_4)_2$, rt, THF/H_2O	47	53
14[c]	$CaCl_2$	$NaBH_4$, rt, dioxane/MeOH	79	21
15[c]	$CaCl_2$	$NaBH_4$, rt, MeOH/THF	87	13

[a] General screening conditions: 0.8 mmol of **1**, 0.8 mmol Lewis acid and 0.8 mmol borohydride in 0.5 M solution of solvent at rt for 20 min unless otherwise stated. [b] Ratio and selectivity determined by GC (see ESI†). [c] 4.0 Equivalents of sodium borohydride.

Table 2 Calcium salt screen under optimised conditions[a]



Entry	Calcium salt	Selectivity[b] 2	3
1	CaF_2	0	100
2	$CaBr_2$ hydrate	79	21
3	$CaCl_2$	87	13
4	CaI_2 hydrate	36	64
5	$Ca(BF_4)_2$	26	74
6	$Ca(OCl_4)_2$ hydrate	91	9
7	$Ca(OMe)_2$	18	82
8	$Ca(OTf)_2$	92	8
9	$Ca(OTs)_2$	48	52
10	$Ca(OPhCl)_2$	73	27
11	$Ca(OMs)_2$	21	79
12	$Ca(OiPr)_2$	18	82
13	$Ca(OC_6H_4OMe)_2$	17	83
14	$Ca(SO_3C_8F_{17})_2$	92	8
15	$Ca(NTf_2)_2$	83	17
16	$Ca(NTf_2)_2$ NBu_4PF_6	91	9

[a] General screening conditions: 0.8 mmol of **1** and 0.8 mmol calcium salt dissolved in MeOH (0.8 mL) and added to a suspension of 3.2 mmol sodium borohydride in THF (9.6 mL). [b] Selectivity was determined by GC.

success was the discovery of a reaction solvent system (THF–MeOH, 12 : 1) which gave high selectivity (87 : 13, **2** : **3**) with a stoichiometric amount of calcium chloride and four equivalents of sodium borohydride (entry 15, Table 1).

With optimised reaction conditions in hand, a broad calcium salt screen was performed to investigate the influence of different calcium salts on the selectivity of the reduction. Using the same conditions as shown in Table 1, entry 13, we found calcium salts basing sulfonate counterions, *e.g.* calcium triflate and $Ca(SO_3C_8F_{17})_2$ (Table 2, entries 8 and 14) to increase the selectivity of the reaction (**2** : **3** was increased up to 92 : 8). Calcium salts with poor solubility in MeOH, such as calcium methoxide, calcium *i*-propoxide, and calcium *p*-methoxyphenolate showed less selectivity for the desired product **2** (Table 2, entries 7, 12, and 13).

In light of the exciting results obtained with calcium triflate, a commercial available calcium salt, we further investigated the ratios of THF and MeOH used in the reaction. It was found, however, that our original conditions (THF–MeOH, 12 : 1) proved to be optimum (see ESI†). The optimised conditions therefore involved adding a methanolic solution of the starting material and one equivalent of calcium triflate to a suspension of four equivalents of sodium borohydride in THF to give an overall ratio of THF–MeOH of 12 : 1.

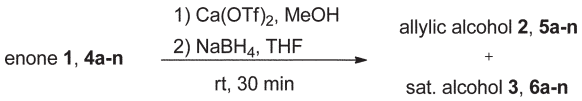
Our developed conditions for the 1,2-reduction was applied to a broad range of substrates, comparing our chemistry to the Luche protocol, and also to the selectivity obtained when solely using sodium borohydride in the absence of an additive (Table 3). The sodium borohydride reduction of β-substituted cyclic α,β-unsaturated ketones without any additive showed moderate selectivity for 1,2-reduction, however, in the presence of calcium triflate, we obtained almost complete selectivity for the majority of substrates. The selectivity for six-membered rings was better than that for five- and seven-membered rings (Table 3, entries 1, 2, and 3). Importantly, our conditions were comparable, or in some cases better (Table 3, entry 9) than the Luche conditions. While selectivity was uniformly high, certain substrates (Table 3, entries 11 and 13) only gave moderate yield. In general, we found this was due to a competing elimination reaction of the resultant allylic alcohol.[15]

Delighted by the broad applicability of our method, we were keen to further its potential applications outside selective 1,2-reduction chemistry. Previously, it has been shown that calcium chloride can mediate the stereoselective reduction of α,β-epoxy ketones, with the epoxide functioning as a stereodirecting group.[16] To the best of our knowledge, an analogous study with α,β-aziridinyl ketones has not been carried out.[17] We have therefore completed preliminary studies, which show that stereoselective reduction of α,β-aziridinyl ketones under our developed conditions is indeed possible and the product is isolated in high diastereoselectivity (Scheme 1).

Conclusions

In conclusion, we have developed a new method to reduce α,β-unsaturated carbonyls selectively with sodium borohydride in the presence of calcium triflate. Even challenging substrates, such as 2-cyclopentenone, were reduced to the corresponding allylic alcohols with very good selectivity. Furthermore, this reaction method is suitable for the stereoselective reduction of α,β-aziridinyl ketones.

Table 3 Substrate scope of reaction conditions



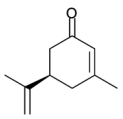
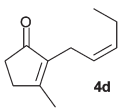
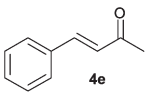
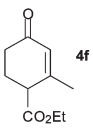
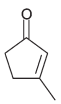
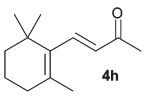
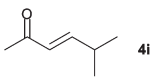
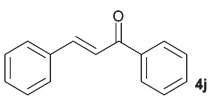
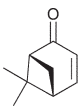
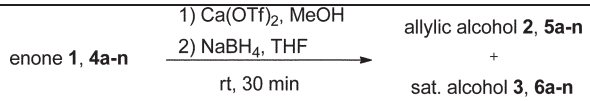
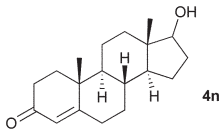
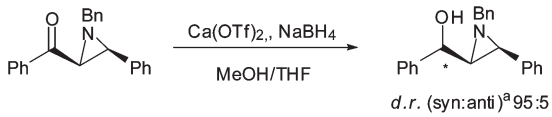
		Selectivity **2**, **5a–n**: **3**, **6a–n**[a]			
Entry	Substrate	$Ca(OTf)_2$	$CeCl_3$	No LA[c]	Yield[b,d] (%)
1	 1	92 : 8	97 : 3	0 : 100	75
2	 4a	99 : 1	99 : 1	50 : 50[e]	96
3	 4b	87 : 13	89 : 11	75 : 25	77
4	 4c	97 : 3	97 : 3	80 : 20	96[h]
5	 4d	98 : 2	99 : 1	67 : 33[f]	69
6	 4e	100 : 0	100 : 0	99 : 1	99
7	 4f CO_2Et	99 : 1	99 : 1	70 : 30[e]	52[i]
8	 4g	99 : 1	99 : 1	38 : 62[g]	78
9	 4h	99 : 1	87 : 13	99 : 1	93
10	 4i	99 : 1	100 : 0	94 : 6	61
11	 4j	99 : 1	100 : 0	92 : 8	44
12	 4k	100 : 0	100 : 0	88 : 12	72[h]
13	 4l	99 : 1	99 : 1	87 : 13	52[h]
14	 4m	100 : 0	100 : 0	90 : 10	79

Table 3 *(Contd.)*



Entry	Substrate	Selectivity **2**, **5a–n**: **3**, **6a–n**[a] $Ca(OTf)_2$	$CeCl_3$	No LA[c]	Yield[b,d] (%)
15	 **4n**	99 : 1	99 : 1	90 : 10	86[h]

[a] Selectivity was determined by GC. [b] Isolated yield. [c] No additive was added [$NaBH_4$ (1.0 equiv.), MeOH, rt]. [d] General reaction conditions: 3 mmol of enone and 3 mmol of calcium triflate dissolved in MeOH (3 mL) was added to 12 mmol sodium borohydride in THF (36 mL). [e] Published results: see ref. 12*b*. [f] Published results: see ref. 14. [g] Published results: see ref. 12*a*. [h] Diastereoselectivities for the following products (determined by ^{1}H NMR): **5c** (d.r. = 95 : 5), **5k** (d.r. = 100 : 0), **5l** (d.r. = 91 : 9), **5n** (d.r. = 93 : 7). [i] d.r. could not be determined.



Scheme 1 Asymmetric reduction of α,β-aziridinyl ketones. [a]Determined by ^{1}H NMR.

Experimental

General procedure to determine the substrate scope

To a suspension of $NaBH_4$ (12.0 mmol) in THF (36 mL) was added in one portion $Ca(OTf)_2$ (3.0 mmol) and enone (3.0 mmol) in MeOH (3 mL). The reaction mixture was stirred for 30 min at rt until TLC indicated consumption of the starting material. The reaction mixture was quenched with H_2O (15 mL) and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography on silica to isolate the desired product.

Acknowledgements

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Notes and references

1 G. A. Molander, *Chem. Rev.*, 1992, **92**, 29; H. C. Aspinall, *Chem. Rev.*, 2002, **102**, 1807; S. Kobayashi, M. Sugiura and H. W. L. Lam, *Chem. Rev.*, 2002, **102**, 2227.
2 S. P. Fricker, *Chem. Soc. Rev.*, 2006, **35**, 524.
3 S. Harder, *Angew. Chem., Int. Ed.*, 2004, **43**, 2714; W. Maudez, M. Meuwly and K. M. Fromm, *Chem.–Eur. J.*, 2007, **13**, 8302; K. Izod, W. Clegg and S. T. Liddle, *Organometallics*, 2000, **19**, 3640; S. Datta, M. T. Gamer and P. W. Roesky, *Organometallics*, 2008, **27**, 1207.
4 S. Harder, *Chem. Rev.*, 2010, **110**, 3852; U. Kazmaier, *Angew. Chem., Int. Ed.*, 2009, **48**, 5790.
5 M. R. Crimmin, I. J. Casely and M. S. Hill, *J. Am. Chem. Soc.*, 2005, **127**, 2042; A. G. M. Barrett, M. R. Crimmin, M. S. Hill and P. A. Procopiou, *Proc. R. Soc. London, Ser. A*, 2010, **466**, 927.
6 M. R. Crimmin, A. G. M. Barrett, M. S. Hill, P. B. Hitchcock and P. A. Procopiou, *Organometallics*, 2007, **26**, 2953; M. R. Crimmin, M. Arrowsmith, A. G. M. Barrett, I. J. Casely, M. S. Hill and P. A. Procopiou, *J. Am. Chem. Soc.*, 2009, **131**, 9670.
7 M. R. Crimmin, A. G. M. Barrtett, M. S. Hill and P. A. Procopiou, *Org. Lett.*, 2007, **9**, 331.
8 S. Datta, P. W. Roesky and S. Blechert, *Organometallics*, 2007, **26**, 4392; S. Datta, M. T. Gamer and P. W. Roesky, *Organometallics*, 2008, **27**, 1207.
9 S. Harder and J. Spielmann, *J. Organomet. Chem.*, 2012, **698**, 7; F. Buch, J. Brettar and S. Harder, *Angew. Chem., Int. Ed.*, 2006, **45**, 2741; J. Spielmann, F. Buch and S. Harder, *Angew. Chem., Int. Ed.*, 2008, **47**, 9434.
10 V. J. Meyer and M. Niggemann, *Eur. J. Org. Chem.*, 2011, 3671; M. Niggemann and M. J. Meel, *Angew. Chem., Int. Ed.*, 2010, **49**, 3684; M. Niggemann and N. Bisek, *Chem.–Eur. J.*, 2010, **16**, 11246; S. Haubenreisser and M. Niggemann, *Adv. Synth. Catal.*, 2011, **353**, 469.
11 Selective examples of asymmetric reactions with alkaline earth metal complexes: S. Kobayashi, T. Tsubogo, S. Saito and Y. Yamashita, *Org. Lett.*, 2008, **10**, 807; T. Tsubogo, S. Saito, K. Seki, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2008, **130**, 13321; H. Van Nguyen, R. Matsubara and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2009, **48**, 5927; S. Saito and S. Kobayashi, *J. Am. Chem. Soc.*, 2006, **128**, 8704; S. Saito, T. Tsubogo and S. Kobayashi, *Chem. Commun.*, 2007, 1236; T. Poisson, T. Tsubogo, Y. Yamashita and S. Kobayashi, *J. Org. Chem.*, 2010, **75**, 963; T. Poisson, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2010, **132**, 7890; S. Kobayashi and Y. Yamashita, *Acc. Chem. Res.*, 2011, **44**, 58; T. Tsubogo, Y. Yamashita and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9117; K. Miura, T. Nakagawa and A. Hosomi, *J. Am. Chem. Soc.*, 2002, **124**, 536; G. Kumaraswamy, M. N. V. Sastry and N. Jena, *Tetrahedron Lett.*, 2001, **42**, 8515; W. Zheng, Z. Zhang, M. J. Kaplan and J. C. Antilla, *J. Am. Chem. Soc.*, 2011, **133**, 3339; T. Suzuki, N. Yamagiwa, Y. Matsuo, S. Sakamoto, K. Yamaguchi, M. Shibasaki and R. Noyori, *Tetrahedron Lett.*, 2001, **42**, 4669; M. J. Vanden Eynden and J. P. Stambuli, *Org. Lett.*, 2008, **10**, 5289.
12 (*a*) J.-L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226; (*b*) J.-L. Luche and A. L. Gemal, *J. Am. Chem. Soc.*, 1981, **103**, 5454; (*c*) J.-L. Luche, L. Rodriguez-Hahn and P. Crabbé, *J. Chem. Soc., Chem. Commun.*, 1978, 601.
13 K. Mikami, M. Terada and H. Matsuzawa, *Angew. Chem., Int. Ed.*, 2002, **41**, 3554.
14 S. Utimoto, *Chem. Lett.*, 1991, 1847.
15 The elimination product of **4j** was identified as (*E*)-(3-chloroprop-1-ene-1,3-diyl)dibenzene (determined by GC/MS and ^{1}H NMR)
16 M. Taniguchi, H. Fujii, K. Oshima and S. Utimoto, *Tetrahedron*, 1995, **51**, 679.
17 Reduction of α,β-epoxy and α,β-aziridinyl yones systems by Noyori Hydrogenation was published recently: V. Druais, C. Meyer and J. Cossy, *Org. Lett.*, 2012, **14**, 516.

