On the reduction of tertiary radicals by samarium diiodide (SmI_2)

Tadamichi Nagashima, Alexey Rivkin, and Dennis P. Curran

Abstract: Reduction of *o*-iodophenyl 3-methylbut-2-enyl ether with samarium diiodide generates mixtures of 3-isopropyl-2,3-dihydrobenzofuran and 3-(2-propenyl)-2,3-dihydrobenzofuran along with a small amount of dimer. If a source of deuterium is present during the reduction, then the 3-isopropyl product predominates and this product is labeled with one deuterium. However, attempts to quench the putative tertiary organosamarium reagent by adding a deuterium source after the reduction were not very successful at room temperature. But at 0°C, the organosamarium reagent was generated (at least to the extent of about 50%, as measured by deuterium quenching), and its decomposition was followed over time by a series of quenching experiments. The results suggest that tertiary radicals are reduced to a significant extent by SmI_2 to form an anionic (presumably alkylsamarium) species. This species is thermally unstable and decomposes to the corresponding reduced and eliminated products. The reduced product is consistently formed in slight excess over the eliminated one, and the mechanism of formation of these products is not yet clear.

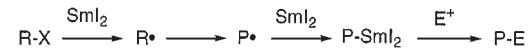
Key words: samarium diiodide, SmI_2, reduction, alkyl samarium.

Résumé : La réduction de l'oxyde d'*o*-iodophényle et de 3-méthylbut-2-ényle par le diiodure de samarium conduit à un mélange de 3-isopropyl-2,3-dihydrobenzofurane et de 3-(prop-2-ényl)-2,3-dihydrobenzofurane en plus de faibles quantités de dimères. Si la réduction se fait en présence d'une source de deutérium. Le produit 3-isopropyle est alors prédominant et il est marqué par un deutérium. Toutefois, tous les essais effectués à la température ambiante en vue de piéger le réactif organosamarium tertiaire putatif par addition d'une source de deutérium après la réduction ont été infructueux. Toutefois, à 0°C, on a généré le réactif organosamarium (au moins jusqu'à un niveau de 50% si l'on se base sur le produit piégé au deutérium) et on a étudié sa décomposition en fonction du temps en faisant appel à des expériences de piégeage. Les résultats suggèrent que le SmI_2 provoque une importante réduction des radicaux tertiaires avec formation d'espèces anioniques (probablement de l'alkylsamarium). Cette espèce est thermiquement instable et elle se décompose pour donner les produits correspondants de réduction et d'élimination. Il y a toujours formation d'une quantité légèrement supérieure de produit réduit par rapport au produit d'élimination et le mécanisme de formation de ces produits n'est toujours pas clair.

Mots clés : diiodure de samarium, SmI_2, réduction, alkylsamarium.

Introduction

Samarium diiodide (SmI_2) is a powerful and soluble reducing agent whose popularity in organic synthesis is continually increasing (1). The use of samarium diiodide to control sophisticated sequences of radical and ionic reactions (2) rests on the understanding of how SmI_2 reacts with functional groups, radicals, and radical ions. It is well demonstrated that the reductions of halides by SmI_2 initially produce radicals (1), and it is now generally accepted that these radicals often can be reduced by another equivalent of SmI_2 to give putative organosamarium intermediates (eq. [1]) (3, 4). Little is known about the structure of these intermediates, and they sometimes have limited stability (4*a*, 5). But they often behave like "carbanions" and combine with reactive electrophiles to give trapped products (1–4).



Reduction by SmI_2 occurs readily for radicals bearing electron withdrawing groups as well as primary alkyl radicals. In contrast, most vinyl and aryl radicals appear to undergo radical–solvent reactions (H-abstraction, addition) faster than they are reduced by SmI_2 (however, when electron withdrawing groups are present, vinyl radicals may be reduced to vinylsamarium reagents. See ref. (6)). The situation with secondary and especially tertiary radicals is less clear. Labeling studies (4*a*, *b*) with electrophiles show that secondary radicals can be reduced to organosamarium reagents, but the trapped products are frequently accompanied by small amounts of products of (apparent) radical disproportionation. Tertiary radicals frequently do not give trapped products at all (4–6). (Qualitatively similar behavior is seen in solid phase reactions. See ref. (7)).

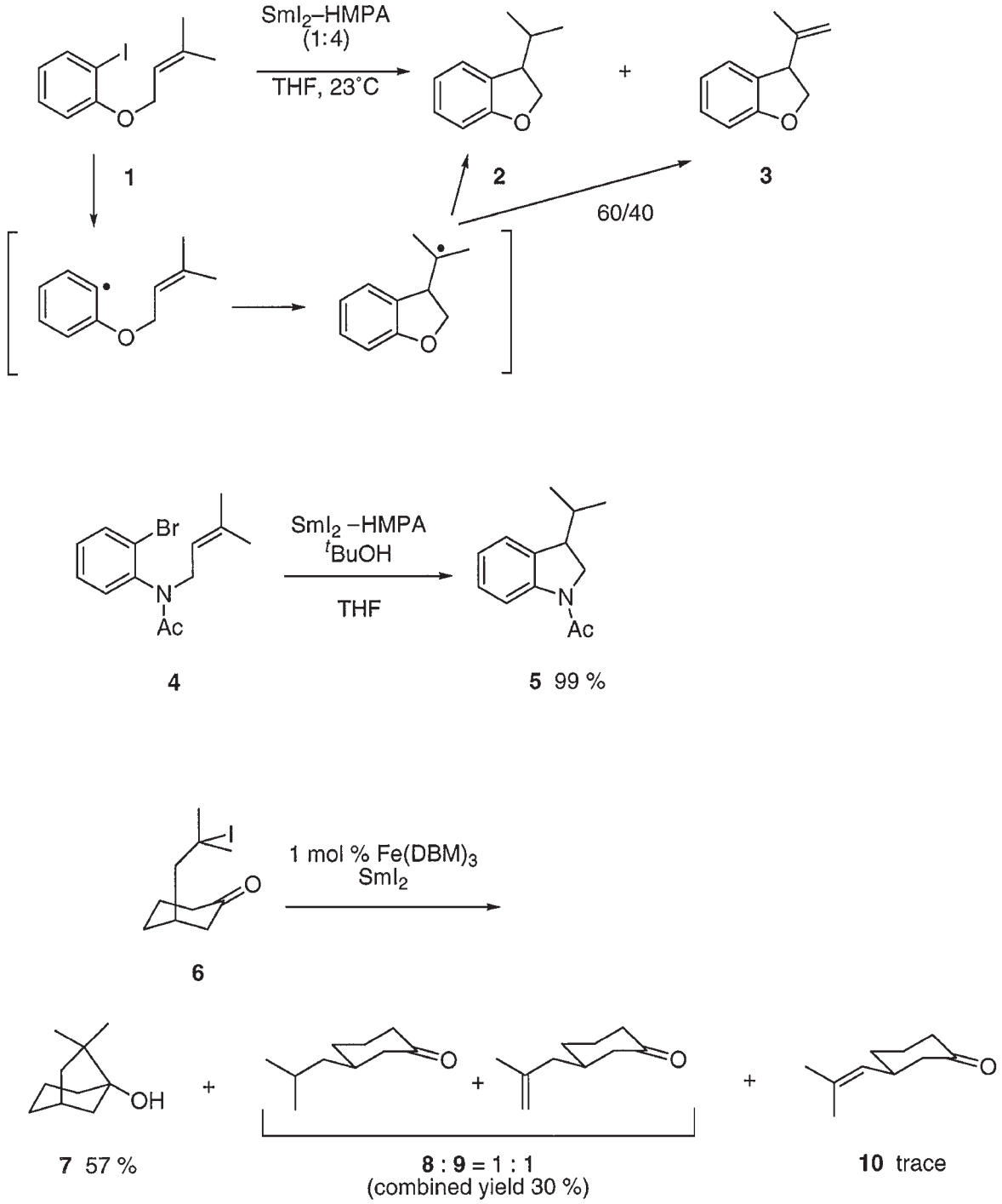
Received September 14, 1999. Published on the NRC Research Press website on June 2, 2000.

We dedicate this paper to Prof. Stephen Hanessian on the occasion of his 65th birthday.

T. Nagashima, A. Rivkin, and D.P. Curran.[1] Department of Chemistry, University of Pittsburgh, Pittsburgh PA 15260, U.S.A.

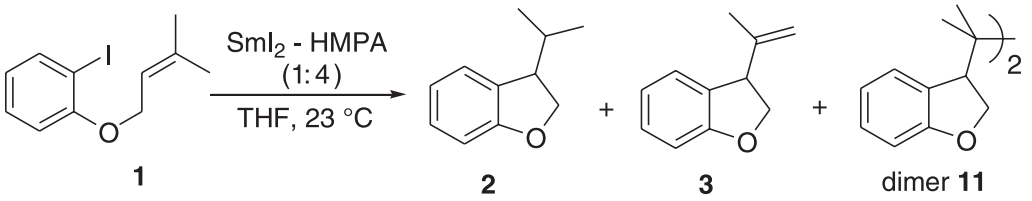
[1]Author to whom correspondence may be addressed. Telephone: (412) 624-8240. Fax: (412) 624-9861. e-mail: curran+@pitt.edu

Fig. 1. Generation and reaction of 3°-radicals by SmI_2. (*a*) See Curran and Totleben (4*b*); (*b*) See Inanaga et al. (8); (*c*) See Molander and McKie (4*c*).



Three key reactions of precursors of tertiary radicals in the presence of SmI_2 are shown in Fig. 1. We reported (4*b*) that the reduction of aryl iodide **1** by SmI_2 in THF/HMPA without a proton source provided products **2** and **3** in a 60:40 ratio and concluded that these products probably resulted from radical disproportionation. This result is typical of other related systems (7). However, Inanaga (8) reported that a very similar reduction of **4** with SmI_2/HMPA in the presence of *tert*-butanol provided **5** in 99% yield. In an intramolecular example, Molander and McKie (4*c*) reported that the reduction of **6** with SmI_2/HMPA in the presence of 1% $Fe(DBM)_3$ gave the cyclized product **7** in 57% yield along with 30% yield of a 1:1 mixture of **8** and **9** (and a trace of **10**). These divergent results are difficult to compare directly due to the different reaction conditions and because the presence of the ketone in **6** may alter the reduction pathway (9), so we decided to undertake a series of experiments designed to probe how tertiary radicals

Table 1. Reduction of **1**. Product study.



Entry	SmI_2/1	Ratio[a] 2:3:11	Combined yield[b]
1	2.2	54 : 43 : 3	85%
2[c]	1.1	53 : 44 : 3	79%

[a]Based on the ^{1}H NMR spectrum of the crude misture.

[b]Based on the weight of the crude mixture.

[c]7% of the iodine **1** was recovered.

react with SmI_2. We show that both in the presence and absence of proton sources, tertiary radicals can be reduced by SmI_2. These resulting anionic species are unstable and decompose to reduced and eliminated products.

Results and discussion

We initially chose to repeat the reduction of **1**. If the products from this reaction are formed exclusively by radical–radical reactions, then **2** and **3** should be formed in a 50:50 (not 60:40) ratio, and there should also be some dimer **11** from radical recombination and perhaps the other possible regioisomeric alkene (not shown) from disproportionation. Formation of products by radical–radical reactions also only requires 1 equiv. of SmI_2, whereas electrophile-trapped products generally consume 2 equiv. of SmI_2. It is known that 4 equiv. of HMPA are required to generate SmI_2 with maximum reducing power (3, 10), and for consistency all reactions in this work employed those conditions. In addition, aqueous quenches were not used in any reactions, since it is also known that SmI_2 does not react rapidly with water and that water increases the reduction potential of SmI_2 (in other words, addition of water tends to promote reductions rather than stopping them (11)). Reactions were quenched by bubbling dry air through the mixture until the color of SmI_2 had dissipated (a few seconds). Data for the initial reductions of **1** are shown in Table 1.

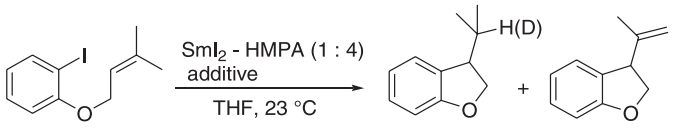
Reduction of **1** with 2.2 equiv. of SmI_2 (Table 1, entry 1) gave results very similar to those reported (4*b*), except that we were now able to carefully separate and characterize a small amount of dimer **11** (as a *meso–d,l*-mixture). The starting iodide **1** was completely consumed in this reaction, even though the characteristic purple color of the SmI_2 never dissipated. Products **2**, **3**, and **11** were formed in 85% combined (isolated) yield in a ratio of 53:44:3. Thus, dimer **11** is formed, but the regioisomeric alkene of **3** (not shown) is not, and there is somewhat more **2** than **3**. The reaction was repeated with 1.1 equiv. of SmI_2 (entry 2), and this time the SmI_2 rapidly decolorized. The same three products were isolated in the same ratio in 79% yield. The starting iodide **1** was recovered in 7% yield, thus accounting for the marginally lower yield.

These results seem reasonably consistent with formation of products by radical reactions, if one hypothesizes that the excess of **2** over **3** can be accounted for by a small amount of two electron reduction followed by protonation (proton source unknown). If about 10% of **2** is formed by two electron reduction, then this could even account for the observation that 1.1 equiv. of SmI_2 was not quite sufficient to consume all of **1**. However, the authentic product ratios of radical–radical reactions are not known, and the results in Table 1 might also be explained by reduction of the tertiary radical to an organosamarium reagent, followed by decomposition to the observed products with regeneration of Sm(II). This decomposition must be quite rapid, otherwise more starting material should have been recovered from experiment 2. This possibility is not unreasonable, since many organometallic species decompose by disproportionation and coupling reactions that do not involve free radicals.

To investigate the effect of proton sources, we next conducted the reduction of **1** in the presence of alcohols, and the results of these experiments are reported in Table 2. Consistent with the results of Inanaga (8), reduction of **1** with 2.2 equiv. SmI_2 in the presence of *tert*-butanol now provided only protonated product **2** in 79% yield (Table 2, entry 1). Neither the alkene **3** nor the dimer **11** was detected. The use of methanol-d_4 provided mostly the reduced product **2** along with a trace of the alkene **3** (ratio 97:3). The yield was somewhat diminished (54%), but **2** contained 89% deuterium at the methine position based on GC–MS analysis (Table 2, entry 2). In two related experiments, **1** was reduced in the absence of methanol, and then methanol-d_4 was added (prior to oxygen quenching) after 30 s and 5 min, respectively, (Table 2, entries 3 and 4). As expected, this gave results similar to entries 1 and 2 of Table 1, although the yields were not quite as high (we did not analyze for the dimer in these experiments). Interestingly, the reduced product **2** contained 7–8% deuterium.

We next ran a series of experiments at 0°C in an effort to see if a more long-lived organosamarium species could be generated. Blank experiments using a slight deficiency of SmI_2 (1.8 equiv.) showed that at 0°C the color dissipated about 30–40 s after the end of the addition of the iodide. Thus, we choose 1 min as the shortest quench to ensure that the deuterium source was not introduced prior to the consumption of the starting material. In a series of experiments, the time between completion of addition of **1** and addition of the quench was extended from 1 min to 180 min, as shown

Table 2. Reduction of **1** with alcohol additives.

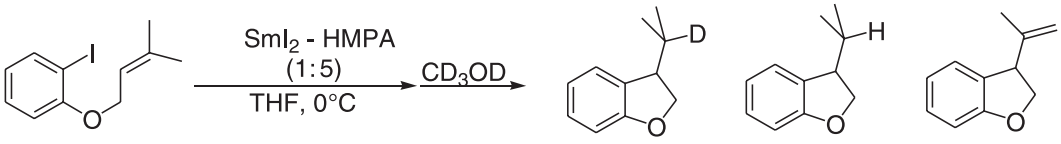


1 (**1** : SmI_2 = 1 : 2.2) **2** **3**

Entry	Additive	Ratio 2:3[b]	Combined yield	%D in **2**
1	^{t}BuOH	**2** only	79%	—
2	CD_3OD	97:3	54%	89[a]
3	After 5 min, CD_3OD	56:44	52%	8[a]
4	After 30 sec, CD_3OD	58:42	68%[c]	7[b]

[a]Based on the ^{1}H NMR spectrum of the crude mixture.
[b]Based on the GC–MS of the crude mixture.
[c]Based on the weight of crude mixture.

Table 3. Reduction of **1** at 0°C with CD_3OD quenching.



1 (**1**:SmI_2 = 1:2.2) **2D** **2H** **3**

Entry	Rxn time (min)[a]	Ratio 2D:2H:3[b]	% Yield (2H+2D+3)[d]
1	0	91:06:03	91
2	1	59:27:14	91
3	2	52:30:18	91
4	4	45:33:22	91
5	5	41:35:24	90
6	10	35:37:28	90
7	20	27:43:30	89
8	30	21:48:31	90
9	40	17:51:32	88
10	50	14:53:33	89
11	60	11:54:35	90
12	180	00:58:42	89

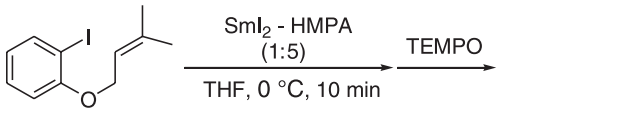
[a]Time between the addition of **1** and CD_3OD.
[b]Based on ^{1}H NMR spectrum.
[c]The CD_3OD was present when **1** was added.
[d]Combined isolated yield.

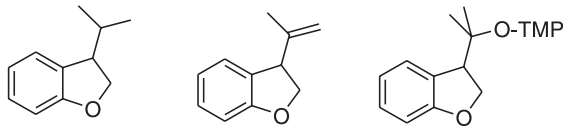
in Table 3, entries 2–12. The Table shows the %D incorporation of **2**D as well as the ratio of **2**D:**2**H:**3**. Accepting that product **2**D is a marker for the formation of an anionic (organosamarium) species, these data show that at least about 60% of **1** is reduced to an anionic species in the absence of an added proton source. Over 3 h, the evolution of this species is revealed by tracing the decrease in the yield of **2**D (to 0%) and the increases in the yield of both **2**H and **3**. Over this time, the combined isolated yield of the three products remains constant (about 90%). Accordingly, the initial 59% of anionic species (reflected by the amount of **2**D in entry 2) decomposed over 3 h to 31% **2**H and 28% **3**.

We have recently shown that organosamarium reagents react with TEMPO (12), so we tried duplicate quenching experiments with TEMPO in place of methanol, as shown in Table 4. In addition to **2** and **3**, these experiments also provided the TEMPO quenched product **12**, although the efficiency of the TEMPO quenching (21–23%) at 10 min is considerably less than that of the MeOD quenching (35°C, see Table 3, entry 6). The experiments also prove that reactions were complete when the alcohol or TEMPO quench was added. A separate experiment showed that addition of **1** and SmI_2 to TEMPO provided recovered starting material **1**; presumably, the TEMPO was reduced by SmI_2.

To complement the quenching studies with deuterated methanol, we next prepared hexa-deutero substrates **13a**, **b** shown in Table 5 (see the Experimental section for their synthesis). These substrates were reduced as usual with 1.1

Table 4. Reduction of **1** at 0°C with TEMPO quenching.



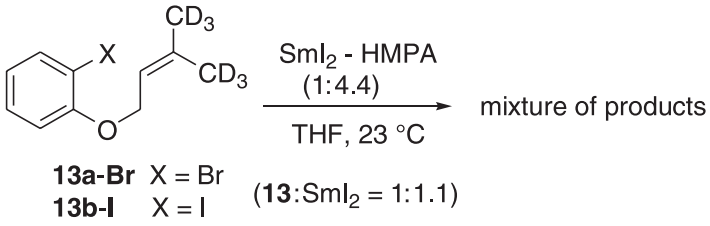


2 **3** **12**

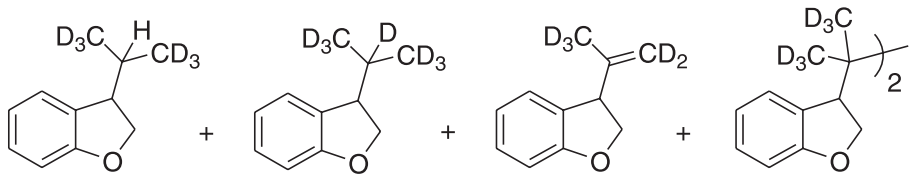
Run	Ratio 1:2:12[a]	Yield of **12**[b]
1	45:32:23	16
2	49:30:21	19

[a]Based on the ^{1}H NMR spectrum of the crude mixture.
[b]Isolated yield.

Table 5. Reduction of deuterated analogs of **1**.



Products



14 **15** **16** **17**

Entry	X	Ratio **14**:**15**:**16**:**17**:**13** (**15**:**16**)[a]
1	I	16:44:34:04:02 (56:44)
2	Br	48:29:23:02:20 (56:44)

[a]Based on ^{1}H NMR spectrum of the product mixture.

equiv. of SmI_2, and then the product ratios were assessed by recording and integrating the crude ^{1}H NMR spectra of the reaction mixtures. The results of these two experiments are shown in Table 5, entries 1,2. While the reduction of the iodide **13b** was instantaneous, the bromide **13a** required 2 h for decolorization of the SmI_2, and 20% unreacted bromide was still recovered after workup. The formation of substantial amounts of d_7 product **15** in both cases clearly shows that protonation cannot account for formation of all the reduced products and that some form of disproportionation is occurring. Interestingly, the reduction of the (less reactive) bromide **13b** gave considerably more of the d_6 (protonated) product **14**. If the increased amount of **14** in the case of bromide was a result of more efficient reduction to the 3°-alkylsamarium reagent, then this could explain why 20% of bromide remained after the samarium was consumed. However, the bromide and iodide must yield the same radical after reduction, so it is unclear how the nature of the original radical precursor can affect the fate of the cyclized radical. Due caution should be exercised in interpreting these experiments due to possible experimental error; in each experiment, the recorded yield of the d_7 product **15** somewhat exceeded that of the d_5 alkene product **16**. This is not possible according to any mechanism, since the average total of deuteria per molecule must be six.

Finally, to gauge the effect of an added ketone, we conducted reduction of **13a** in the presence of ketone **18** (Fig. 2). This experiment is complicated because the ketone

Fig. 2. Coreduction of **13a** and a ketone.

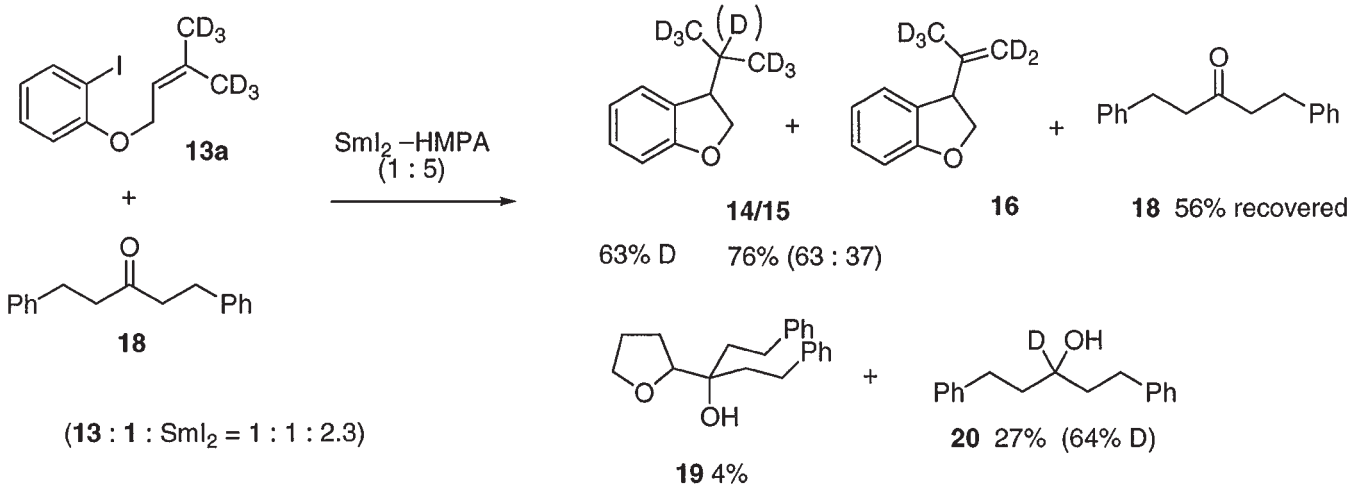
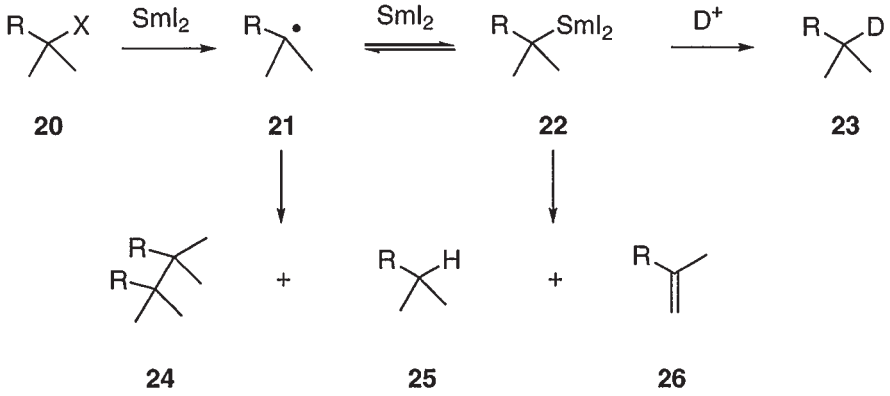


Fig. 3. Pathways for product formation reduction of 3°-halides by SmI_2.



can be reduced in competition with the iodide. As before, disproportionation products **14**/**15**/**16** were produced and the reduction product **14**/**15** contains a significant amount (63%) of deuterium in the methine position. The ratio of reduced product **14**/**15** to alkene **16** is also higher than in the experiments without the ketone. As for the fate of the ketone **16** itself, 56% is recovered unchanged while 4% is trapped as the THF adduct **19** (this product is thought to result from H-abstraction from the THF followed by reduction to an organosamarium reagent and addition to the ketone) (4). About 27% of ketone **18** is reduced to alcohol **20**. In turn, this alcohol also contains 64% D, showing that there is a significant pathway for transfer of allyl hydrogen from **13a**.

Conclusions

The results in this paper provide new insights into the behavior of tertiary radicals in the presence of SmI_2. Some of the possible reaction pathways are illustrated in Fig. 3. Tertiary radical **21** could directly recombine and disproportionate to give the observed products **24**–**26**. Alternatively, it could be reduced to a tertiary alkylsamarium species **22**, which in turn provides the final products either by protonation (to give **23**) in competition with bimolecular disproportionation (to give **24**–**26**) and (or) homolysis back to the radical **21** (that is, the reduction step is reversible). In either case, an equivalent of Sm(II) must be regenerated in tandem with disproportionation.

When the reduction is carried out in the presence of a proton source at either 25°C or 0°C, a good yield of the labeled, reduced product **23** is formed. This strongly suggests that the tertiary organosamarium species **22** is formed. Whether or not the organosamarium species **22** is formed when the reduction is conducted in the absence of proton source is less clear. While proton sources are known to boost the reduction potential of SmI_2 in the absence of HMPA (11), the strong ligating capabilities of HMPA for Sm (10) suggest that it would dampen or eliminate any effect of added proton sources. If this is correct, then the reductions in the absence of the proton source should also provide the tertiary alkyl samarium reagent **22**, and we interpret our inability to efficiently trap this intermediate by subsequent addition of a proton source as due to its instability with respect to disproportionation. Supporting this analysis are the results of the study at 0°C (Table 3), in which a significant amount of the organosamarium reagent was generated and its decomposition to the disproportionation products was followed over time.

While the results support the postulate that a substantial amount of the products derive from alkylsamarium reagents,

they certainly do not exclude the formation of some products through radical reactions. For example, the dimer **24** may form through a radical recombination (although we cannot exclude the possibility of coupling of organosamarium reagents), and the inability to ever observe quantitative deuterium incorporation in the reduced product **23** may point to the occurrence of radical hydrogen transfer reactions from the solvent. In addition, the mechanism of the decomposition of the intermediate organosamarium reagent **22** is also not clear. This reagent could return to the radical **21** by the reverse of the reduction or it could decompose by a number of ionic pathways. At this point, the radical pathway seems less likely since the ratio of disproportionation products to recombination products is higher than that for typical tertiary radicals.

In summary, tertiary halides are not very cooperative partners in a number of C—C bond forming processes mediated by SmI_2. In the past, this has been interpreted by us and others as due to the inability of SmI_2 to reduce 3°-radicals to samarium reagents. Our new results suggest that SmI_2 is more efficient at reducing 3°-radicals than previously thought, and that the problems with subsequent bond forming reactions arise due to the instability of the samarium reagents, which disproportionate over a period of minutes or less at room temperature.

Experimental

Typical procedure for the reduction of *O*-prenyl-2-iodophenol (1) by SmI_2–HMPA in the absence of electrophile

HMPA (0.60 mL, 3.45 mmol) was added to SmI_2 (0.10 M in THF, 8.8 mL, 0.88 mmol) at 23°C. After 1 h, *O*-prenyl-2-iodophenol **1** (0.116 g, 0.402 mmol) in THF (0.7 mL) was added. After 21 h, dry air was bubbled through the mixture until the color changed to light brown and then 0.1 N HCl (20 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL). The combined ether layers were washed with 5% $Na_2S_2O_3$ (1 × 20 mL), sat. NH_4Cl (1 × 20 mL), and brine (1 × 20 mL), and were dried over $MgSO_4$. The ratio of the products (**2**, **3**, and **11**) was determined by recording the ^1H NMR spectrum of the crude mixture. The products were purified by flash chromatography (SiO_2, hexanes/EtOAc = 15:1) to give the dimer **11** (1.6 mg, 2% yield) and a mixture (34.4 mg) of 3-(2-propyl)-2,3-dihydrobenzofuran (**1**) and 3-(propen-2-yl)-2,3-dihydrobenzofuran (**2**). The ratio of these products was determined by ^1H NMR spectrum of the mixture.

(*dl*,*meso*)-2,3-Bis(2,3-dihydrobenzofuran-3-yl)-2,3-dimethylbutane (11)

^1H NMR (300 MHz, $CDCl_3$) (mixture of *dl* and *meso*) δ: 7.23 (2 H, d, *J* = 7.5 Hz), 7.19–7.09 (2 H, m), 6.91–6.77 (8 H, m), 4.78–4.66 (2 H, m), 4.42 (2 H, q, *J* = 9.4 Hz), 3.55 (1 H, dd, *J* = 8.6, 1.6 Hz), 3.48 (1 H, dd, *J* = 9.0, 3.1 Hz), 1.05 (3 H, s), 1.00 (3 H, s), 0.95 (3 H, s), 0.84 (3 H, s). MS (EI) *m*/*z*: 322, 238, 161, 119. HRMS (EI) *m*/*z*: Anal. calcd. for $C_{22}H_{26}O_2$ 322.1933; found: 322.1923.

Typical procedure for the reduction of *O*-prenyl-2-iodophenol (1) in the presence of a proton source

HMPA (0.25 mL, 1.44 mmol) was added to SmI_2 (0.10 M in THF, 3.3 mL, 0.33 mmol) at 23°C. After 30 min, ^{t}BuOH (16 μL, 0.17 mmol) was added, and 5 min later, *O*-prenyl-2-iodophenol (**1**) (42.7 mg, 0.148 mmol) in THF (0.5 mL) was added in one portion at 23°C. After 30 min, dry air was bubbled for 1 min, and then 0.1 N HCl (10 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL). The combined ether layers were washed with 5% $Na_2S_2O_3$ (1 × 10 mL), sat. NH_4Cl (1 × 15 mL), and brine (1 × 15 mL), and were dried over $MgSO_4$. The mixture was passed through a SiO_2 column (eluent: hexanes/Et_2O = 2:1) to give 3-(2-propyl)-2,3-dihydrobenzofuran (**2**) (19.0 mg, 0.117 mmol, 79% yield).

General procedure for the reduction of *O*-prenyl-2-iodophenol (1) by SmI_2–HMPA with CD_3OD quenching

To SmI_2 (0.10 M in THF, 40.0 mL, 4.00 mmol) was added HMPA (3.5 mL, 20 mmol) at 23°C. After 1 h, 3.82 mL of the mixture was transferred to another flask, and cooled to 0°C. A solution of *O*-prenyl-2-iodophenol (**1**) (50 mg, 0.17 mmol) in THF (0.3 mL) was added dropwise over the period of 20 s, and 5 min later, CD_3OD (0.2 mL, 4.9 mmol) was added. After 2 min, air was bubbled through the mixture until the color turned to yellow. After the addition of 0.1 N HCl (5 mL), the mixture was extracted with Et_2O (3 × 5 mL). The combined ether layers were concentrated and the mixture was passed through a short SiO_2 column (eluent: dichloromethane) to give a mixture of products (25.3 mg). The product ratio was determined by ^1H NMR spectrum of the mixture.

Ethyl 3-trideuteriomethyl-4,4,4-trideuterio-2-butenoate

Triethyl phosphonoacetate (20.5 mL, 10.3 mmol) was added dropwise into a suspension of NaH (2.15 g, 89.6 mmol) in THF 100 mL at 0°C. After 5 min, the cooling bath was removed. After 1.5 h, acetone-d_6 (8.0 mL, 0.11 mol) was added. After 2 h, the mixture was poured into 10% NH_4Cl (500 mL), and was extracted with Et_2O (1 × 100 mL and 2 × 50 mL). The combined ether layers were washed with sat. NH_4Cl (1 × 50 mL) and brine (1 × 50 mL), and were dried over $MgSO_4$. The product was purified by distillation (bp = 76.0–76.5°C at 54 mmHg) to give the product (7.57 g, 56.4 mmol, 62% based on NaH). IR (film)(cm^{-1}): 1694, 1144. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.66 (1 H, s), 4.13 (2 H, q, *J* = 7.1 Hz), 1.26 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.21 (s), 155.72 (s), 115.95 (d), 58.97 (t), 26.0 (m), 18.8 (m), 13.97 (q). MS (EI) *m*/*z*: 134, 106, 89, 83. HRMS (EI) m/*z*: Anal. calcd. for $C_7H_6D_6O_2$ 134.1214; found: 134.1254.

3-Trideuteriomethyl-4,4,4-trideuterio-2-buten-1-ol

DIBALH (1.0 M in hexane, 100 mL, 0.10 mol) was added dropwise to a solution of the above ester (6.76 g, 50.4 mmol) in CH_2Cl_2 (50 mL) at 0°C. After 1.5 h, MeOD (6 mL) was added dropwise. After the mixture became cloudy, sat. potassium sodium tartrate (25 mL) was added. The mixture was poured into Et_2O (150 mL), and 2 N HCl (150 mL) was added. After the separation, the aqueous layer was extracted with Et_2O (1 × 100 mL). The combined organic

layers were washed with 1 N HCl (1 × 50 mL) and brine (2 × 25 mL), and were dried over $MgSO_4$. The product was purified by distillation at normal pressure (bp = 129–139°C) to give alcohol (3.12 g, 33.9 mmol, 67%). IR (film) (cm^{-1}): 3322, 1101, 1070. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.41 (1 H, t, *J* = 7.1 Hz), 4.20–4.08 (2 H, m), 1.20 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.37 (s), 123.76 (d), 58.88 (t), 24.5 (m), 17.0 (m). MS (EI) *m/z*: 92, 74. HRMS (EI) *m/z*: Anal. calcd. for $C_5H_4D_6O$ 92.1108; found: 92.1114.

O-(3-Trideuteriomethyl-4,4,4-trideuterio-2-buten-1-yl)-2-iodophenol (13b)

Diethyl azodicarboxylate (2.96 g, 17.0 mmol) in THF (2 mL) was added into a mixture of 2-iodophenol (3.52 g, 16.0 mmol), PPh_3 (4.20 g, 16.0 mmol), and the above prenyl alcohol-d_6 (1.39 g, 15.1 mmol) in THF (35 mL) at 0°C. The temperature was gradually raised to 23°C. After 16 h, most of the solvent was removed under reduced pressure, and pentane (100 mL) was added to give a precipitate. After the removal of the precipitate by filtration, the product was purified by flash chromatography (SiO_2, hexanes/Et_2O = 30:1) to give **13b** (3.05 g, 10.4 mmol, 69% yield). IR (film) (cm^{-1}): 1469, 1275, 1239, 1016, 748. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.77 (1 H, dd, *J* = 7.7, 1.6 Hz), 7.28 (1 H, dt, *J* = 8.5, 1.6 Hz), 6.82 (1 H, dd, *J* = 8.2, 0.9 Hz), 6.70 (1 H, dt, *J* = 1.1, 7.6 Hz), 5.51 (1 H, t, *J* = 6.5 Hz), 4.58 (2 H, d, *J* = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.38, 139.68, 137.68, 129.30, 122.38, 119.52, 112.57, 86.89, 66.16, (two CD_3 carbons were not detected). MS (EI) *m/z*: 294, 221, 75. HRMS (EI) *m/z*: Anal. calcd. for $C_{11}H_7D_6IO$ 294.0388; found: 294.0382.

1-[2-(2,3-Dihydrobenzofuran-3-yl)propyl-2-oxy]-2,2,6,6-tetra-methylpiperidine (12)

HMPA (4.0 mL, 23 mmol) was added to SmI_2 (0.1 M in THF, 44.0 mL, 4.40 mmol) at 23°C. After 14 min, the mixture was cooled to 0°C, and *O*-prenyl-2-iodophenol (**1**) (0.576 g, 2.00 mmol) in THF (2 mL) was added dropwise over the period of 2 min. After 10 min, TEMPO (0.943 g, 6.04 mmol) in THF (1 mL) was added in one portion. After 1 min, a mixture of sat. potassium sodium tartrate (10 mL), sat. $NaHCO_3$ (5 mL), and 5% $Na_2S_2O_3$ (5 mL) was added, and the mixture was extracted with Et_2O (3 × 15 mL). The combined ether layers were washed with 5% $Na_2S_2O_3$ (1 × 15 mL), a mixture of sat. potassium sodium tartrate and sat. $NaHCO_3$ (5 mL each, 1 ×), H_2O (2 × 15 mL), and brine (1 × 15 mL), and were dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, hexanes/Et_2O = 10:1) to give **12** (0.122 g, 0.385 mmol, 19% yield). IR (film) (cm^{-1}): 1483, 1460, 1375, 1364, 1234, 1132, 748.; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.33 (1 H, d, *J* = 7.3 Hz), 7.13 (1 H, t, *J* = 7.4 Hz), 6.83 (1 H, t, *J* = 7.0 Hz), 6.78 (1 H, d, *J* = 8.0 Hz), 4.73 (1 H, dd, *J* = 9.5, 5.5 Hz), 4.54 (1 H, t, *J* = 9.6 Hz), 3.94 (1 H, dd, *J* = 9.5, 5.4 Hz), 1.68–1.45 (4 H, m), 1.38 (3 H, s), 1.37–1.26 (2 H, m), 1.16 (3 H, s), 1.154 (3 H, s), 1.146 (3 H, s), 1.12 (3 H, s), 1.11 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.10 (s), 128.75 (s), 128.36 (d), 125.72 (d), 119.99 (d), 109.54 (d), 80.90 (s), 73.34 (t), 59.56 (s), 59.43 (s), 53.25 (d), 40.96 (t), 35.23 (q), 35.13 (q), 23.71 (q), 23.32 (q), 23.71 (q), 23.32 (q), 21.03 (q), 20.90 (q), 17.18 (t). MS (CI) *m/z*: 318 [M + H], 157, 142.

O-(3-Trideuteriomethyl-4,4,4-trideuterio-2-buten-1-yl)-2-bromo-phenol (13a)

Diethyl azodicarboxylate (2.96 g, 17.0 mmol) in THF (2 mL) was added into a mixture of 2-bromophenol (2.78 g, 16.1 mmol), PPh_3 (4.20 g, 16.0 mmol), and the above alcohol (1.38 g, 15.0 mmol) in THF (40 mL) at 0°C. The temperature was gradually raised to 23°C. After 17.5 h, most of the solvent was removed under reduced pressure, and pentane (100 mL) was added to give a precipitate. After the removal of the precipitate by filtration, the product was purified by flash chromatography (SiO_2, hexanes/Et_2O = 10:1) followed by distillation (bp = 90–98°C at 0.2 mmHg) to give **13a** (2.64 g, 10.7 mmol, 71% yield). IR (film) (cm^{-1}): 1476, 1276, 1030, 744 ^1H NMR (300 MHz, $CDCl_3$) δ: 7.54 (1 H, dd, *J* = 7.7, 1.6 Hz), 7.24 (1 H, dt, *J* = 1.6, 7.4 Hz), 6.90 (1 H, dd, *J* = 8.3, 1.1 Hz), 6.82 (1 H, dt, *J* = 1.5, 7.7 Hz), 5.51 (1 H, t, *J* = 6.6 Hz), 4.60 (2 H, d, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.11, 137.21, 128.26, 121.60, 119.40, 113.52, 112.19, 65.93, (two CD_3 carbons were not detected). MS (EI) *m/z*: 248, 246, 228, 188, 186, 175, 173. HRMS (EI) *m/z*: Anal. calcd. for $C_{11}H_7D_6BrO$ 246.0526; found: 246.0490.

General procedure for the reduction of *O*-prenyl(d_6)-2-halophenol 13a, b by SmI_2–HMPA

To SmI_2 (0.10 M in THF, 11.0 mL, 1.10 mmol) was added HMPA (0.85 mL, 4.89 mmol) at 23°C. After 20 min, *O*-prenyl(d_6)-2-iodophenol (**13a**) (0.299 g, 1.02 mmol) in THF (1 mL) was added. After 8 h, dry air was bubbled until the mixture turned to yellow, and then 0.1 N HCl (15 mL) was added. After the extraction with Et_2O (3 × 10 mL), the combined ether layers were washed with 5% $Na_2S_2O_3$ (1 × 10 mL), 0.1 N HCl (1 × 10 mL), and brine (1 × 10 mL), and were dried over $MgSO_4$. The crude mixture was passed through a SiO_2 column (eluent: hexanes/Et_2O = 10:1) to give a mixture of products (0.130 g). The products ratio was determined by ^1H NMR spectrum of the mixture.

SmI_2 reduction of *O*-prenyl(d_6)-2-iodophenol (13a) in the presence of the ketone 18

HMPA (0.95 mL, 5.5 mmol) was added to SmI_2 (0.1 M in THF, 11.0 mL, 1.10 mmol) at 23°C. After 50 min, a mixture of *O*-prenyl(d_6)-2-iodophenol (**13a**) (0.142 g, 0.483 mmol) and 1,5-diphenylpentan-3-one (**18**) (0.120 g, 0.504 mmol) in THF (1 mL) was added in one portion. After 1 h, dry air was bubbled through the mixture, and then 0.1 N HCl (15 mL) and brine (5 mL) were added. After the extraction with Et_2O (3 × 10 mL), the combined ether layers were washed with 5% $Na_2S_2O_3$ (1 × 10 mL), 0.1 N HCl (1 × 10 mL), and brine (1 × 10 mL), and were dried over $MgSO_4$. The products were separated by flash chromatography (SiO_2, hexanes/EtOAc = 10:1 – 5:1) to give a mixture of 3-(2-propyl)-2,3-dihydrobenzofuran (d_6 and d_7) (**14** and **15**) and 3-(propen-2-yl)-2,3-dihydrobenzofuran (d_5) (**16**) (61.1 mg), a mixture of 1,5-diphenyl-3-pentanol (**20**) and 1,5-diphenyl-3-(2-tetrahydrofuranyl)-3-pentanol (**19**) (39.1 mg), and 1,5-diphenyl-3-pentanone (**18**) (67.0 mg, 56% recovery).

1,5-Diphenyl-3-(tetrahydrofuran-2-yl)pentan-3-ol (19)

The authentic sample of **19** was prepared as follows: HMPA (0.95 mL, 5.46 mmol) was added to SmI_2 (0.1 M in

THF, 11 mL, 1.1 mmol) at 23°C. After 40 min, a mixture of iodobenzene (0.334 g, 1.64 mmol) and 1,5-diphenylpentan-3-one (**18**) (113.9 mg, 0.478 mmol) in THF (1 mL) was added. After 21 h, 0.1 N HCl (15 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL). The combined ether layers were washed with 5% $Na_2S_2O_3$ (1 × 10 mL), 0.1 N HCl (1 × 10 mL), and brine (1 × 10 mL), and dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 5:1 – 3:1) to give **19** (0.124 g, 0.398 mmol, 83% yield). IR (film) (cm^{-1}): 3461, 1495, 1453, 1066, 749, 699.; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.37–7.13 (10 H, m), 3.94–3.77 (3 H, m), 2.83–2.57 (4 H, m), 2.08 (1 H, s), 2.07–1.82 (7 H, m), 1.73 (1 H, dt, J = 5.3, 12.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.56 (s), 142.44 (s), 128.49 (d), 128.42 (d), 125.94 (d), 125.81 (d), 83.32 (d), 74.47 (s), 68.58 (t), 38.89 (t), 36.59 (t), 30.27 (t), 29.79 (t), 26.27 (t), 25.59 (t). MS (EI) *m*/*z*: 239, 91. HRMS (EI) *m*/*z*: Anal. calcd. for $C_{17}H_{19}O$ [M – C_4H_7O] 239.1436; found: 239.1437.

Acknowledgments

We thank the National Institutes of Health for funding this work.

References

1. (*a*) A. Krief and A.M. Laval. Chem. Rev. **99**, 745 (1999); (*b*) R. Nomura and T. Endo. Chem. Eur. J. **4**, 1605 (1998); (*c*) G.A. Molander. *In* Comprehensive organic synthesis. Vol. 1. *Edited by* B.M. Trost and I. Fleming. Pergamon, Oxford. 1991. p. 251. (*d*) F.A. Khan and R. Zimmer. J. Prakt. Chem. Chem. Ztg. **339**, 101 (1997); (*e*) M. Murakami and Y. Ito. J. Organometal. Chem. **473**, 93 (1994); (*f*) G.A. Molander. *In* Organic reactions. Vol. 46. *Edited by* L.A. Paquette. Wiley, N.Y. 1994. p. 211. (*g*) G.A. Molander. Chem. Rev. **92**, 29 (1992); (*h*) J.A. Soderquist. Aldrichimica Acta, **24**, 15 (1991).
2. (*a*) G.A. Molander amd C.R. Harris. Tetrahedron, **54**, 3321 (1998); (*b*) T. Skrydstrup. Angew. Chem. Int. Ed. Eng. **36**, 345 (1997); (*c*) G.A. Molander and C.R. Harris. Chem. Rev. **96**, 307 (1996); (*d*) D.P. Curran and R.L. Wolin. Synlett. 317 (1991); (*e*) T.L. Fevig, R.L. Elliott, and D.P. Curran. J. Am. Chem. Soc. **110**, 5064 (1988).
3. E. Hasegawa and D.P. Curran. Tetrahedron Lett. **34**, 1717 (1993).
4. (*a*) D.P. Curran, T.L. Fevig, C.P. Jasperse, and M.J. Totleben. Synlett. 943 (1992); (*b*) D.P. Curran and M.J. Totleben. J. Am. Chem. Soc. **114**, 6050 (1992); (*c*) G.A. Molander and J.A. McKie. J. Org. Chem. **56**, 4112 (1991).
5. G.A. Molander and J.A. McKie. J. Org. Chem. **58**, 7216 (1993).
6. M. Hojo, H. Harada, J. Yoshizawa, and A. Hosomi. J. Org. Chem. **58**, 6541 (1993).
7. (*a*) X.H. Du and R.W. Armstrong. J. Org. Chem. 62, 5678 (1997); (*b*) X.H. Du and R.W. Armstrong. Tetrahedron Lett. **39**, 2281 (1998).
8. J. Inanaga, O. Ujikawa, and M. Yamaguchi. Tetrahedron Lett. **32**, 1737 (1991).
9. D.P. Curran, X. Gu, W. Zhang, and P. Dowd. Tetrahedron, **53**, 9023 (1997).
10. (*a*) M. Shabangi and R.A. Flowers. Tetrahedron Lett. **38**, 1137 (1997); (*b*) M. Shabangi, J.M. Sealy, J.R. Fuchs, and R.A. Flowers. Tetrahedron Lett. **39**, 4429 (1998).
11. E. Hasegawa and D.P. Curran. J. Org. Chem. **58**, 5008 (1993).
12. T. Nagashima and D.P. Curran. Synlett. 330 (1996).