## Letter

# Metal-Mediated Debromination of *gem*-Dibromoalkenes under Mild Conditions

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**Abstract** We describe the facile and efficient metal-promoted reduction of C–Br bonds of *gem*-dibromides. When the reaction is mediated by indium, the corresponding vinyl bromides are obtained in good yields and high *E*-stereoselectivities. Alternatively, when the reduction is mediated by samarium diiodide, vinyl bromides are obtained in moderate yields and good *Z*-selectivities.

**Key words** dehalogenation, reduction, indium, samarium, vinyl bromides, stereoselectivity

Both (*E*)- and (*Z*)-vinyl bromides are extremely useful tools in organic chemistry.<sup>1</sup> In the last decade, their use as coupling partners in a wide range of transition metal-mediated cross-coupling reactions has sparked a great deal of interest in their stereoselective synthesis.<sup>2</sup> Consequently, a number of reagents have been reported that provide either (*Z*)-<sup>3</sup> or (*E*)-vinyl bromides.<sup>4</sup> These transformations perform well in a number of favorable cases; however, polyfunctionalized substrates can give unsatisfactory results.

The reduction of *gem*-dibromides, readily available from the reaction of an aldehyde with carbon tetrabromide and triphenylphosphine, presents a practical alternative to the synthesis of vinyl bromides. Only a few examples of the hydrogenolysis of 1,1-dibromo-1-alkenes have been reported in the literature.<sup>5</sup> For this reason, the introduction of simpler reagents and more-general experimental conditions is still needed.

Since its introduction by Kagan and co-workers in 1977,<sup>6</sup> samarium diiodide has been used to perform a wide variety of organic reactions because of its versatility in oneand two-electron transfer processes. Barbier-type C–C bond formations,  $\beta$ -eliminations, and reductions with Sml<sub>2</sub> have been widely investigated.<sup>7</sup> An interesting feature of this reagent is the regulation of the reduction potential of SmI<sub>2</sub> by using various solvents or additives. This makes samarium diiodide an attractive reducing agent, because of the possibility of tuning its reactivity and selectivity.<sup>8</sup> Simple reductions of organic monohalides with SmI<sub>2</sub> are very common in the literature.<sup>9</sup> In contrast to the reactions of monohalides, reactions of *gem*-dihalides with SmI<sub>2</sub> are very limited. To the best of our knowledge, there is just one example of a reduction of *gem*-dibromoalkenes with SmI<sub>2</sub> in benzene containing 10% hexamethylphosphoramide to afford rearranged alkynes.<sup>10</sup>

On the other hand, indium has attracted much attention from organic chemists due to its low toxicity, environmental benefits, and great synthetic potential.<sup>11</sup> Additions to carbonyl compounds are probably the most common indium-promoted reactions in organic synthesis.<sup>12</sup> Recently, indium has emerged as a useful reducing agent in several organic reactions, such as dehalogenations<sup>13</sup> and reductive eliminations.<sup>14</sup> In this regard, we have recently reported the indium-promoted dehalogenation of *gem*-dibromoalkenes to give vinyl bromides in an ionic-liquid medium. Despite the excellent results achieved, the reaction was quite slow under normal heating and it required ohmic heating to go to completion in one to three hours.<sup>15</sup>

Here, we describe the details of both the indium- and samarium-mediated reduction reactions of 1,1-dibromo-1alkenes to give vinyl bromides, including their mechanism, scope, and limitations.

Based on our preliminary results, the reduction of 1-(2,2-dibromovinyl)-2-methylbenzene (**1a**) was assessed (Scheme 1). We initially investigated the use of Sm(II) as a reducing agent under various conditions, and the results are compiled in Table 1.

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Scheme 1 Reductive debromination of 1-(2,2-dibromovinyl)-2-methylbenzene (1a)

Thus, *gem*-dibromoalkene **1a** was treated with Sml<sub>2</sub> (2.0 equiv) in THF in the presence of H<sub>2</sub>O (20.0 equiv with respect to Sml<sub>2</sub>) as an additive. Samarium diiodide was prepared without difficulty as a 0.1 M solution in THF by sonication of 1,2-diiodoethane and metallic samarium.<sup>16</sup> Reaction at room temperature for three hours afforded the desired bromoalkene **2a** in moderate yield and good *Z*-selectivity (Table 1, entry 1). Increasing the temperature to reflux, resulted in a steep decrease in both the yield and selectivity (entry 2). In contrast, lowering the temperature to 0 °C had no effect on either the yield or the selectivity (entry 3). On the other hand, prolonging the reaction time to 24 hours resulted in a slight increase in the selectivity, but had no effect in the yield (entry 4).

We then turned our attention to the use of indium as a reducing agent. Our initial studies focused on the reduction of 1-(2,2-dibromovinyl)-2-methylbenzene (**1a**) by employing a combination of indium and a co-reductant in the presence of an additive in aqueous THF. When a solution of *gem*-dibromoalkene **1a** in THF-H<sub>2</sub>O (1:1 v/v) was treated with indium powder (2.0 equiv) and Cul (0.5 equiv) in the presence of catalytic amounts of iodine, and the resulting mixture was heated to reflux for three hours, the desired bromoalkene **2a** was obtained in moderate yield and moderate *E*-selectivity (Table 1, entry 5). Decreasing the temperature to room temperature resulted in a lower conversion to the desired vinyl bromide (entry 6). The use of

 $Pd(PPh_3)_4$  as an additive led to poorer results in terms of both yield and selectivity (entry 7). However, when  $InCl_3$ was used as a co-reductant in the presence of  $Pd(PPh_3)_4$ , reduction of *gem*-dibromoalkene **1a** occurred at room temperature in three hours, giving 1-bromoalkene **2a** in excellent yield and moderate *E*-stereoselectivity (entry 8). Increasing the amount of indium metal (2.0 equiv) led to an increase in the yield (entry 9). Note that both the co-reductant and the additive are essential for efficient progress of

the reaction (entries 10 and 11). Having established the optimal conditions, we investigated the reduction of a wide range of structurally varied *gem*-dibromoalkenes to the corresponding vinyl bromides. Thus, reduction of *gem*-dibromoalkenes **1b**,**c** with SmI<sub>2</sub> (2.0 equiv) and H<sub>2</sub>O (40.0 equiv) in THF for three hours<sup>17</sup> afforded the corresponding vinyl bromides **2b**,**c** in moderate yields and moderate *Z*-selectivities (Table 2, entries 1 and 3).

Alternatively, treatment of a solution of a gem-dibromoalkene **1b**-i with indium (2 equiv) and  $InCl_3$  (0.5 equiv) in the presence of tetrakis(triphenylphosphine)palladium(0) (5.0 mol%) in a 1:1 (v/v) mixture of THF and H<sub>2</sub>O at room temperature for three hours<sup>18</sup> gave the corresponding vinyl bromide **2b**-i<sup>19</sup> in good yield and good *E*-selectivity (Table 2, entries 2–10). In addition, no overreduction of the resulting vinyl bromide was observed with any substrate. Reduction of the less reactive cycloaliphatic dibromoalkene **1j** was unsuccessful under both sets of reaction conditions (entries 11 and 12).

The contrasting stereochemical outcome of the indiumand samarium-mediated reductions can be explained in terms of the different mechanisms of the two processes.

A possible mechanistic pathway for the samarium-mediated reduction is shown in Scheme 2. Generation of an

| Entry | $M^1$            | Equiv | M <sup>2</sup>    | Equiv | Additive                           | Equiv | Solvent                    | Temp (° | C) Time (h) | Yieldª (%) | $E/Z^{\rm b}$ |
|-------|------------------|-------|-------------------|-------|------------------------------------|-------|----------------------------|---------|-------------|------------|---------------|
| 1     | $Sml_2$          | 2     | -                 | -     | H <sub>2</sub> O                   | 40    | THF                        | 25      | 3           | 55         | 20:80         |
| 2     | Sml <sub>2</sub> | 2     | -                 | -     | H <sub>2</sub> O                   | 40    | THF                        | 75      | 3           | 11         | 50:50         |
| 3     | Sml <sub>2</sub> | 2     | -                 | -     | H <sub>2</sub> O                   | 40    | THF                        | 0       | 3           | 54         | 20:80         |
| 4     | Sml <sub>2</sub> | 2     | -                 | -     | H <sub>2</sub> O                   | 40    | THF                        | 25      | 24          | 55         | 16:84         |
| 5     | In               | 2     | Cul               | 0.5   | I <sub>2</sub>                     | 0.1   | THF-H <sub>2</sub> O (1:1) | 75      | 3           | 67         | 75:25         |
| 6     | In               | 2     | Cul               | 0.5   | I <sub>2</sub>                     | 0.1   | THF-H <sub>2</sub> O (1:1) | 25      | 3           | 19         | 75:25         |
| 7     | In               | 2     | Cul               | 0.5   | $Pd(PPh_3)_4$                      | 0.05  | THF-H <sub>2</sub> O (1:1) | 75      | 3           | 51         | 70:30         |
| 8     | In               | 1     | InCl <sub>3</sub> | 0.5   | $Pd(PPh_3)_4$                      | 0.05  | THF-H <sub>2</sub> O (1:1) | 25      | 3           | 76         | 75:25         |
| 9     | In               | 2     | InCl <sub>3</sub> | 0.5   | Pd(PPh <sub>3</sub> ) <sub>4</sub> | 0.05  | THF-H <sub>2</sub> O (1:1) | 25      | 3           | 88         | 76:24         |
| 10    | In               | 2     | InCl <sub>3</sub> | 0.5   | -                                  | -     | THF-H <sub>2</sub> O (1:1) | 25      | 3           | -          | -             |
| 11    | In               | 2     | -                 | -     | $Pd(PPh_3)_4$                      | 0.05  | THF-H <sub>2</sub> O (1:1) | 25      | 3           | -          | -             |

Table 1 Conditions for the Synthesis of 1-(2-Bromovinyl)-2-methylbenzene (2a)

<sup>a</sup> Isolated yield.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture.

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| Entry | Reactant | R  | Method <sup>a</sup> | Product | Yield⁵<br>(%) | E/Z <sup>c</sup> |
|-------|----------|--|---------------------|---------|---------------|------------------|
| 1     | 1b       | Ph   | А                   | 2b      | 91            | 60:40            |
| 2     | 1b       | Ph   | В                   | 2b      | 51            | 25:75            |
| 3     | 1c       | $2-MeC_6H_4$   | А                   | 2c      | 88            | 68:32            |
| 4     | 1c       | $2-MeC_6H_4$   | В                   | 2c      | 52            | 22:78            |
| 5     | 1d       | $4-MeOC_6H_4$  | В                   | 2d      | 69            | 60:40            |
| 6     | 1e       | 2-CIC <sub>6</sub> H <sub>4</sub>                      | В                   | 2e      | 89            | 77:23            |
| 7     | 1f       | 2,3,4-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> | В                   | 2f      | 75            | 58:42            |
| 8     | 1g       | 1-naphthyl   | В                   | 2g      | 81            | 59:41            |
| 9     | 1h       | CH=CHPh  | В                   | 2h      | 87            | 55:45            |
| 10    | 1i       | 3-BnOC <sub>6</sub> H <sub>4</sub>                     | В                   | 2i      | 84            | 63:37            |
| 11    | 1j       | cycloheptyl  | А                   | 2j      | -             | -                |
| 12    | 1j       | cycloheptyl  | В                   | 2j      | -             | -                |

<sup>a</sup> Method A: SmI<sub>2</sub> (200 mol%), THF-H<sub>2</sub>O (10:1); B: In (200 mol%), InCl<sub>3</sub> (50 mol%), Pd(PPh<sub>3</sub>)<sub>4</sub> (5.0 mol%), THF-H<sub>2</sub>O (1:1). <sup>b</sup> Isolated yield of analytically pure product.

<sup>c</sup> Determined by 300 MHz <sup>1</sup>H NMR spectroscopy of the crude reaction mixture.

alkenyl radical 3 by single-electron transfer from SmI<sub>2</sub>, followed by reaction of this intermediate radical with SmI<sub>2</sub> should afford the isomeric alkenylsamarium species 4. Isomer 4a should be formed preferentially due to the steric hindrance of the Sm(III) coordination sphere and the R group in isomer 4b. Finally, hydrolysis of the alkenylsamarium 4 should give the corresponding bromoalkene with Zselectivity.



With regard to the mechanism of the indium-mediated reduction, in contrast to the SmI<sub>2</sub>-mediated reaction, we propose the formation of the intermediate vinyl anion 5 (Scheme 3). Protonation of **5** should preferentially give the

thermodynamically more stable (E)-bromoalkene. The benefits of using Pd(PPh<sub>3</sub>)<sub>4</sub> as an additive in the indium-mediated dehalogenation reaction have been previously reported by ourselves<sup>13c</sup> and others.<sup>14b</sup> Even though the role of Pd(0) is not clear, it is probably involved in Pd insertion into the C-Br bond, which would facilitate the metalation.



Scheme 3 Proposed mechanism for the indium(I)-mediated reaction

In conclusion, we have described the synthesis of 1-bromoalkenes by metal-mediated reduction of gem-dibromoalkenes. When the reduction is mediated by samarium diiodide in the presence of water, bromoalkenes are obtained in moderate yields and good Z-selectivities. On the other hand, when the reaction is promoted by an indium metal/indium trichloride combination in the presence of tetrakis(triphenylphosphine)palladium(0), the corresponding bromoalkenes are obtained in good yields and high Eselectivities.

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# Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561558.

# **References and Notes**

- (1) The Chemistry of Dienes and Polyenes; Vol. 1; Rappoport Z., Wiley: Chichester, 1997.
- (2) (a) Concellón, J. M.; Rodríguez-Solla, H.; Huerta, M.; Pérez-Andrés, J. A. Eur. J. Org. Chem. 2002, 1839. (b) Vedejs, E.; Peterson, M. J. Top. Stereochem. 1994, 21, 1. (c) Chen, J.; Tao, W.; Zhao, K. Tetrahedron Lett. 1994, 35, 2827. (d) Björkling, F.; Norin, T.; Unelius, R. Synth. Commun. 1985, 15, 463. (e) Pasto, D. J.;

# Synlett

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Taylor, R. T. Org. React. (N. Y.) **1991**, 41, 91. (f) Miller, R. B.; McGarvey, G. J. Org. Chem. **1978**, 43, 4424. (g) Brown, H. C.; Hamaoka, T.; Ravindran, N. J. Am. Chem. Soc. **1973**, 95, 6456.

- (3) Takai, K.; Nitta, K.; Utimoto, K. J. Am. Chem. Soc. **1986**, 108, 7408.
- (4) (a) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. Bull. Chem. Soc. Jpn. **1989**, 62, 143. (b) Abbas, S.; Hayes, C. J.; Worden, S. Tetrahedron Lett. **2000**, 41, 3215.
- (5) (a) Uenishi, J.; Kawahama, R.; Yonemitsu, O. J. Org. Chem. 1998, 63, 8965. (b) Ranu, B. C.; Samanta, S.; Guchhait, S. K. J. Org. Chem. 2001, 66, 4102.
- (6) (a) Namy, J. L.; Girard, P.; Kagan, H. B. Nouv. J. Chem. 1977, 1, 5.
  (b) Girard, P.; Namy, J. L.; Kagan, H. B. J. Am. Chem. Soc. 1980, 102, 2693.
- (7) Concellón, J. M.; Rodríguez-Solla, H. Chem. Soc. Rev. 2004, 33, 599.
- (8) Steel, P. G. J. Chem. Soc., Perkin Trans. 1 2001, 2727.
- (9) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. Synlett 1992, 943.
- (10) Kunishima, M.; Hioki, K.; Ohara, T.; Tani, S. J. Chem. Soc., Chem. Commun. **1992**, 219.
- (11) For reviews on indium chemistry, see: (a) Cintas, P. Synlett 1995, 1087. (b) Li, C. J. Tetrahedron 1996, 52, 5643. (c) Marshall, J. A. Chemtracts: Org. Chem. 1997, 10, 481. (d) Li, C. J. In Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes; Anastas, P.; Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998, Chap. 14. (e) Paquette, L. A. In Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes; Anastas, P.; Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998, Chap. 14. (e) Paquette, L. A. In Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes; Anastas, P.; Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998, Chap. 15. (f) Li, C. J.; Chan, T. K. Tetrahedron 1999, 55, 11149.
- (12) Allylations: (a) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. Org. Lett. 2000, 2, 847. (b) Tan, K.-T.; Chang, S.-S.; Cheng, H.-S.; Loh, T.-P. J. Am. Chem. Soc. 2003, 125, 2958. Propargylations: (c) Isaac, M. B.; Chan, T.-H. J. Chem. Soc., Chem. Commun. 1995, 1003. Alkynylations: (d) Augé, J.; Lubin-Germain, N.; Seghrouchni, L. Tetrahedron Lett. 2002, 43, 5255.

Nitromethylations: (e) Soengas, R. G.; Silva, A. M. S. *Synlett* **2012**, *23*, 873. (f) Rodríguez-Solla, H.; Soengas, R. G.; Alvaredo, N. *Synlett* **2012**, *23*, 2083.

- (13) (a) Podlech, J.; Maier, T. C. Synthesis 2003, 633. (b) Ranu, B. C.; Dutta, P.; Sarkar, A. J. Chem. Soc., Perkin Trans. 1 1999, 1139.
  (c) Acúrcio, R.; Soengas, R. G.; Silva, A. M. S. Synlett 2014, 25, 1561.
- (14) (a) Soengas, R. G.; Rodríguez-Solla, H.; Díaz-Pardo, A.; Acúrcio, R.; Concellón, C.; del Amo, V.; Silva, A. M. S. *Eur. J. Org. Chem.* **2015**, 2524. (b) Cho, S.; Kang, S.; Keum, G.; Kang, S. B.; Han, S.-Y.; Kim, Y. *J. Org. Chem.* **2003**, 68, 180.
- (15) Soengas R. G., Silva V. L. M.: Pinto, J.; Rodríguez-Solla, H.; Silva, A. M. S. *Eur. J. Org. Chem.* **2016**, 99.
- (16) Concellón, J. M.; Rodríguez-Solla, H.; Bardales, E.; Huerta, M. *Eur. J. Org. Chem.* **2003**, 1775.
- (17) Samarium-Promoted Reduction of *gem*-Dibromoalkenes 1 (Method A); General Procedure

A 0.1 M solution of SmI<sub>2</sub> in THF (0.8 mmol) was added to a stirred solution of the appropriate *gem*-dibromoalkene **1** (0.4 mmol) in THF (5 mL). Deoxygenated H<sub>2</sub>O (0.5 mL) was added and the mixture was stirred at r.t. for 3 h. The reaction was quenched with 0.1 M aq HCl (10 mL) and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL). The combined organic extracts were washed with sat. aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo.

#### (18) Indium-Promoted Reduction of gem-Dibromoalkenes 1 (Method B); General Procedure Indium metal (90 mg, 0.8 mmol), InCl<sub>3</sub> (88 mg, 0.4 mmol), and Pd(PPh<sub>2</sub>)<sub>4</sub> (18 mg, 2 mol%) were added to a solution of the gem-

Pd(PPh<sub>3</sub>)<sub>4</sub> (18 mg, 2 mol%) were added to a solution of the *gem*dibromoalkene **1** (0.4 mmol) in THF–H<sub>2</sub>O (1:1; 6 mL), and the mixture was stirred at r.t. for 3 h. The reaction was quenched with 1 M aq HCl (3 mL) and the mixture was diluted with H<sub>2</sub>O (25 mL) and extracted with Et<sub>2</sub>O (3 × 25 mL). The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure.

(19) The physical data for compounds **2** were similar to those reported in the corresponding literature; see refs. 2 and 3.

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