ORGANIC
LETTERS

2013
Vol. 15, No. 11
2826–2829

Reductive Bromine Atom-Transfer Reaction

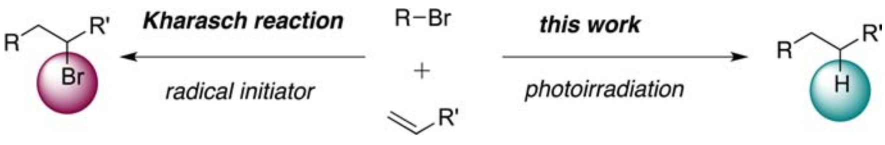
Shuhei Sumino, Akira Fusano, and Ilhyong Ryu*

Department of Chemistry, Graduate School of Science, Osaka Prefecture University,
Sakai, Osaka 599-8531, Japan

ryu@c.s.osakafu-u.ac.jp

Received April 24, 2013

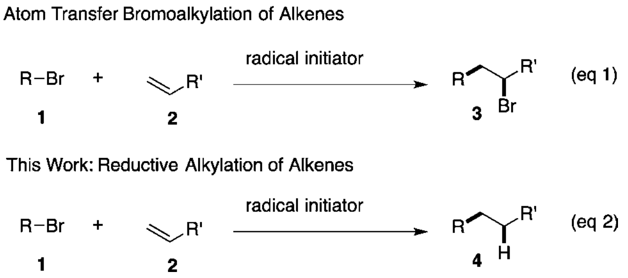
ABSTRACT



Atom-transfer radical (ATR) reactions of alkenes with R−X usually give products having new C−C and C−X bonds at the adjacent carbons. However, when the reaction was carried out under irradiation using a low-pressure Hg lamp, addition/reduction products were obtained in good yield. Hydrogen bromide, formed by H-abstraction of a bromine radical from alkenes, is likely to play a key role in the reductive ATR reaction.

Ever since Kharasch's work published in 1940s,[1] atom-transfer radical (ATR) reactions have found widespread uses in organic synthesis[2] and polymer synthesis.[3] ATR reactions of alkenes and alkynes provide a useful tool to create C−C and C−X bonds across C−C double and triple bonds.[4−6] Whereas archetypal ATR reactions require radical initiators, some ATR reactions of alkyl iodides are known to proceed under light irradiation conditions in the absence of radical initiators.[7]

Scheme 1. Concept: Reductive ATR Reaction of RBr


Atom Transfer Bromoalkylation of Alkenes

This Work: Reductive Alkylation of Alkenes

Generally, ATR reactions of alkyl bromides require more forcing conditions for the initiation than that of alkyl iodides due to the stronger C−X bond. To cleave C−Br bonds, photoirradiation with a low pressure mercury lamp is known to be effective and we recently applied this methodology to the radical addition reaction of alkyl bromides to formaldehyde.[8] In this paper, the radical addition reaction of α-bromo esters and ketones **1** onto alkenes **2** was studied under photoirradiation conditions using a low pressure mercury lamp. The reaction proceeded

---

(1) (a) Kharasch, M. S.; Skell, P. S.; Fisher, P. *J. Am. Chem. Soc.* **1948**, *70*, 1055. (b) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *Science* **1945**, *102*, 128.

(2) (a) Curran, D. P. *Synthesis* **1988**, 489. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (c) Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, Chapter 1.5.

(3) Pintauer, T.; Matyjaszewiski, K. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; Wiley-VCH: Weinheim, 2012; Vol. 4, Chapter 62.

(4) (a) Curran, D. P.; Chen, M. H.; Spletzer, E.; Seong, C. M.; Chang, C. T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (b) Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 9401. (c) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.

(5) (a) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1998**, 1351. (b) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041. (c) Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2001**, *66*, 7776.

(6) (a) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3460. (b) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755. (c) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587. (d) Schär, P.; Renaud, P. *Org. Lett.* **2006**, *8*, 1569. (e) Weidner, K.; Giroult, A.; Panchaud, P.; Renaud, P. *J. Am. Chem. Soc.* **2010**, *132*, 17511.

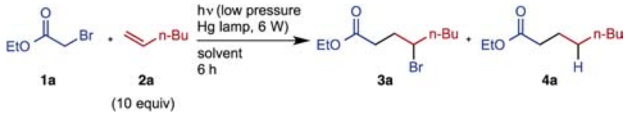
(7) (a) Davies, T.; Haszeldine, R. N.; Tipping, A. E. *J. Chem. Soc., Perkin Trans. 1* **1980**, 927. (b) Tsuchii, K.; Imura, M.; Kamada, N.; Hirao, T.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 6658. (c) Slodowicz, M.; Barata-Vallejo, S.; Vázquez, A.; Nudelman, N. S.; Postigo, A. *J. Fluorine Chem.* **2012**, *135*, 137.

(8) Kawamoto, T.; Fukuyama, T.; Ryu, I. *J. Am. Chem. Soc.* **2012**, *134*, 875.

10.1021/ol4011536

well, but to our surprise it gave the reduced addition products **4** rather than **3** as major product (Scheme 1, eq 2). A literature survey showed that only one precedence exists for "reductive" ATR reaction, which was found in the reaction of 1-bromo-1-chloro-2,2,2-trifluoroethane and allylaromatics with sodium dithionite in MeCN/H_2O solution.[9] In this paper, we present the unusual reductive ATR reaction, which serves as the hydroalkylation of alkenes.

Table 1. Reductive ATR Reaction[a]

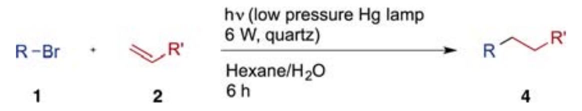


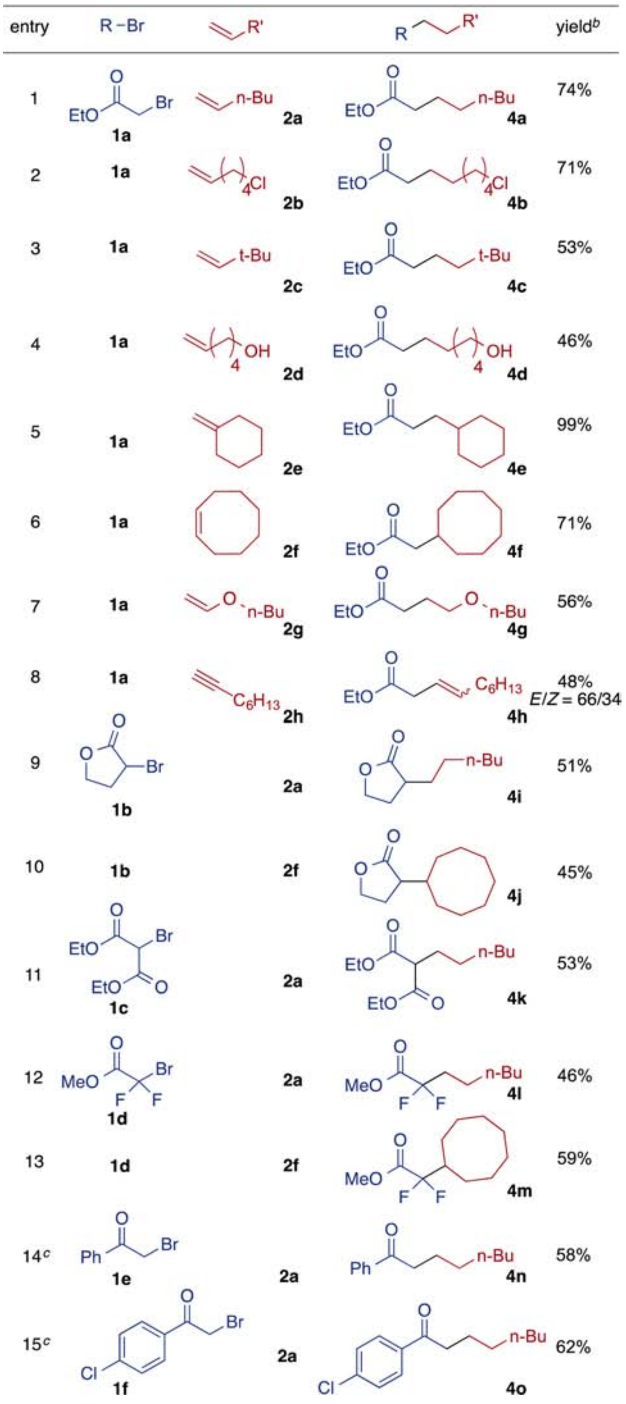
entry	conc of **1a** (M)	solvent (mL)	filter	yield (%) **3a**[b]	yield (%) **4a**[c]
1	0.1	C_6H_6 (5)	quartz	16	59
2	0.1	C_6H_6 (5)	Pyrex	0	0
3[d]	0.1	C_6H_6 (5)	quartz	18	54
4	0.1	MeCN (5)	quartz	4	52[b]
5	0.1	hexane (5)	quartz	21	62
6	0.1	hexane/H_2O (5/0.05)	quartz	16	69
7	0.025	hexane/H_2O (10/0.1)	quartz	4	74

[a] Conditions: **1a** (0.5 mmol), **2a** (5 mmol), solvent (5 mL), hν (low-pressure mercury lamp, 6 W, quartz), 6 h. [b] NMR yield. [c] Isolated yield. [d] The reaction was performed for 12 h under irradiation of 500 W xenon lamp.

We examined the reaction of ethyl α-bromoacetate (**1a**) and 1-hexene (**2a**) as a model reaction under a variety of conditions (Table 1). When a benzene solution of **1a** (0.1 M) and **2a** (10-fold excess) was irradiated using a low-pressure mercury lamp (6 W) through a quartz glass tube, ethyl caprylate (**4a**) was obtained in a 59% yield together with 16% yield of the brominated ATR product **3a** (Table 1, entry 1). The photoirradiation reaction did not proceed when a Pyrex filter was used (Table 1, entry 2). The suitability of a xenon lamp (500 W) was also tested and gave a similar result to that of the mercury lamp (Table 1, entry 3). Among the solvents tested, hexane plus a small amount of water gave the best yield (Table 1, entry 6). Reducing the concentration of [**1a**] = 0.025 M also contributed to increase the yield up to 74% (Table 1, entry 7).

Table 2. Reaction of α-Bromo Carbonyl Compounds and Olefins[a]





entry	R–Br	alkene	product	yield[b]
1	**1a**	**2a**	**4a**	74%
2	**1a**	**2b**	**4b**	71%
3	**1a**	**2c**	**4c**	53%
4	**1a**	**2d**	**4d**	46%
5	**1a**	**2e**	**4e**	99%
6	**1a**	**2f**	**4f**	71%
7	**1a**	**2g**	**4g**	56%
8	**1a**	**2h**	**4h**	48% E/Z = 66/34
9	**1b**	**2a**	**4i**	51%
10	**1b**	**2f**	**4j**	45%
11	**1c**	**2a**	**4k**	53%
12	**1d**	**2a**	**4l**	46%
13	**1d**	**2f**	**4m**	59%
14[c]	**1e**	**2a**	**4n**	58%
15[c]	**1f**	**2a**	**4o**	62%

[a] The reaction was performed by using **1** (0.25 mmol), **2** (2.5 mmol), and hexane/H_2O (10 mL/100 μL) for 6 h under photoirradiation conditions. [b] Isolated yield. [c] 25 mmol of **2a** was used.

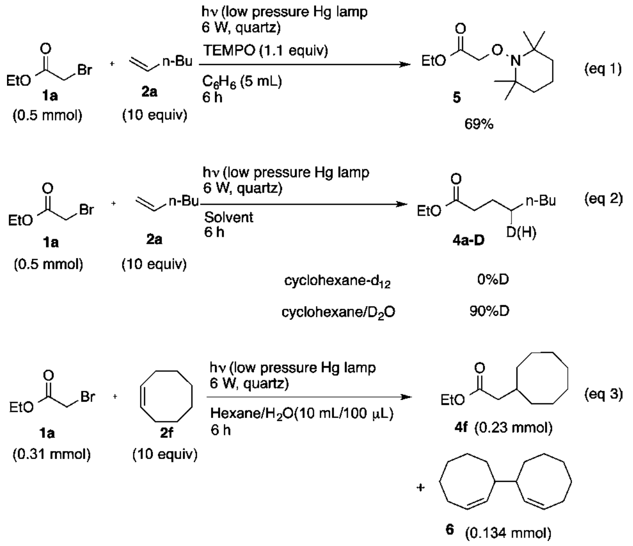
With optimized reaction conditions (Table 1, entry 7) in hand, we then examined the generality of the reductive ATR reaction using a variety of alkyl bromides **1** and alkenes **2**, the results of which are summarized in Table 2. The reaction of **1a** and terminal alkenes **2a**, **2b**, **2c**, and **2d** gave good to modest yields of the expected reductive ATR products **4a**, **4b**, **4c**, and **4d**, respectively (Table 2, entries 1–4). The reaction of **1a** with methylenecyclohexane (**2e**) proceeded smoothly to give the adduct **4e** quantitatively (Table 2, entry 5). Disubstituted alkene **2f** gave **4f** in 71% yield (Table 2, entry 6). Vinyl ether **2g** and 1-octyne (**2h**) also participated in the reductive ATR reaction, giving **4g** and **4h** respectively in modest yields (Table 2, entries

---

[9] (a) Ignatowska, J.; Dmowski, W. *J. Fluorine Chem.* **2006**, *127*, 720. (b) Dmowski, W. *J. Fluorine Chem.* **2011**, *132*, 504.

7 and 8). Cyclic α-bromo ester **1b** and α-bromo-malonate **1c** also gave the corresponding addition/reduction products (Table 2, entries 9−11). Reaction of methyl bromodifluoroacatate (**1d**) with **2a** and **2f** gave **4l** and **4m**, respectively (Table 2, entries 12 and 13). On the other hand, the reaction of α-bromo acetophenone (**1e**) with 1-hexene under standard conditions gave **4n** in very low yield due to the formation of acetophenone, the directly reduced product. When a large excess of 1-hexene (100 fold) was used, **4n** was obtained in a 58% yield (Table 2, entry 14). Under the same conditions, α-bromo ketone **1f** gave **4o** in 62% yield (Table 2, entry 15).

Scheme 2. Experiments To Investigate the Reaction Mechanism



To gain some insight into the reaction mechanism, we conducted several experiments whose results are shown in Scheme 2. The addition of of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the reaction of **1a** with **2a** completely suppressed the formation of product (**4a**), instead giving the TEMPO adduct **5** in 69% yield (Scheme 2, eq 1). This suggested that homolysis of the C−Br bond by photoirradiation worked well in the present system. To determine the source of hydrogen at the 3-position, we carried out deuterium-labeling experiments (Scheme 2, eq 2). Whereas no deuterium incorporation was observed from cyclohexane-d_{12}, added as the solvent, the addition of deuterium oxide caused the deuteration at the 3-position with a D/H ratio of 90:10. On the basis of these observations, we speculated that HBr would be generated by abstraction of the allylic hydrogen of the alkene by bromine radical which acts as radical scavenger,[10] given that the D/H scrambling of HBr by D_2O is quite rapid. To further support this scenario, we were able to detect dimer **6** formed from 2-cyclooctenyl radical, in the reaction of **1a** with **2f** (Scheme 2, eq 3).

Taking these observations together, we propose a nonchain radical reaction mechanism for the unusual reductive ATR reaction (Figure 1). First, photoinduced homolysis of C−Br bond of **1a** would take place to give alkyl radical **A** and Br radical. While **A** would add to alkene to form a new radical **B**, Br radical would abstract hydrogen from the allylic position of alkene to give HBr and allyl radical **C**, which would then undergo dimerization to give **D**.[11] Radical **B** abstracts hydrogen from HBr to give the product **E** and the liberated Br radical would again abstract hydrogen from another molecule of alkene. In this reaction, the addition of water suppressed the reaction of alkene with HBr. Recently, the Wood group[12] and the Renaud group[13] reported that trialkylborane/water or *B*-alkylcatecholborane/methanol complexes, respectively, can serve as effective H atom donors. In this regard, we are now curious about the possibility of using a HBr/water complex, such as **F**, to serve as a good hydrogen donor.[14]

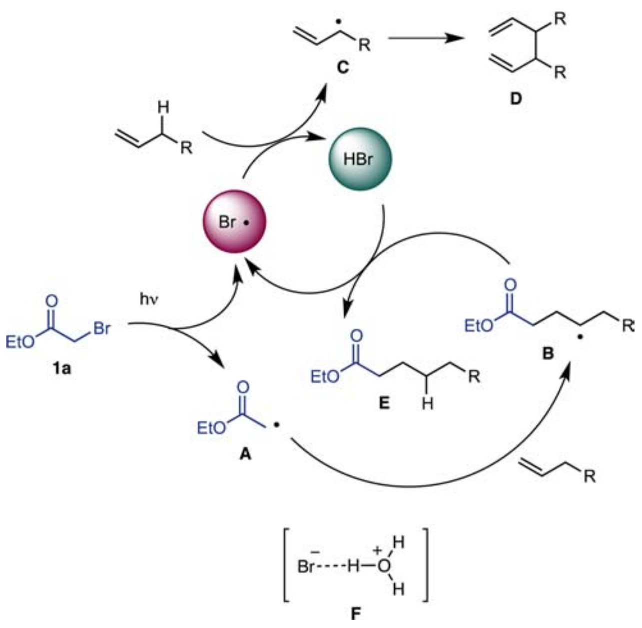


Figure 1. Possible reaction mechanism.

In summary, we have demonstrated the unusual reductive atom-transfer addition of R−Br to alkenes under photoirradiation conditions. The interplay of C−C bond-forming reaction and reduction in the absence of any reducing reagent is an interesting feature of the present reaction. We propose a nonchain radical mechanism involving C−Br homolysis and rapid conversion of the resulting bromine radical to HBr by H-abstraction of alkenes. We are now exploring other applications of bromine radical mediated

---

(10) Matsubara, H.; Tsukida, M.; Ishihara, D.; Kuniyoshi, K.; Ryu, I. *Synlett* **2010**, 2014.

(11) For bromine radical abstraction of hydrogen from the allylic position, see; Kharasch, M. S.; Schwartz, D.; Nudenberg, W. *J. Org. Chem.* **1953**, *18*, 337.

(12) Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513.

(13) (a) Pozzi, D.; Scanlan, E. M.; Renaud, P. *J. Am. Chem. Soc.* **2005**, *127*, 14204. (b) Povie, G.; Marzorati, M.; Bigler, P.; Renaud, P. *J. Org. Chem.* **2013**, *78*, 1553.

(14) We thank a reviewer for calling our attention to this possibility.

reductive C–C bond-forming reactions and the precise role of water in this reaction.

Acknowledgment. I.R. acknowledges MEXT and JSPS for funding of this work.

Supporting Information Available. Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.