CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200901487

Multi-Product Classes Obtained from Allylation of α-Halo Ketones with Allylzinc Bromide

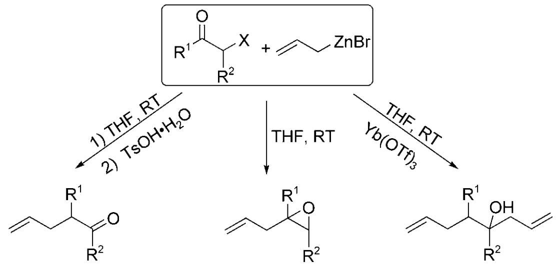
Min Zhang, Yuanyuan Hu, and Songlin Zhang*[a]

Selectivity in organic synthesis is of particular significance due to the high probability of potential parallel (side)reaction pathways or the generation of intermediates, which lead to different product classes. Although several examples have successfully demonstrated this synthesis strategy,[1] little attention has actually been paid to this challenge.

Epoxides—being important building blocks and intermediates[2] in organic synthesis—attracted our attention due to their high reactivity, which allows easy transformation into different products.[3] One of the useful transformations is the Meinwald rearrangement from epoxides to afford aldehydes or ketones.[4]

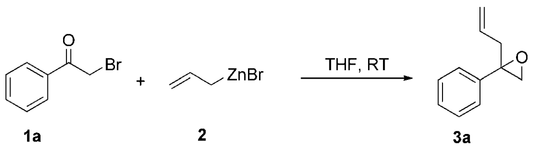
Zinc is a relatively non-toxic metal available at low cost. Although almost ignored for more than 100 years after their discovery, organozinc reagents are today one of the most useful class of organometallic reagents for organic and organometallic synthesis.[5] The lower reactivity of organozinc compounds, once considered a major impediment, has now become one of their greatest assets.[6] Intrigued by the palladium-catalyzed reaction of α-halo ketones with allyl-substituted tin compounds such as allytributyltin or diallyldibutyltin to allylic epoxides,[7] and the indium-mediated allylation of α-chlorocarbonyl compounds[8] to afford homoallylic chlorohydrins which transferred to the corresponding epoxides in the second-step under basic conditions, we tried to investigate the possible epoxide formation from the allylation of α-halo ketones with allylzinc bromide. We also anticipated that the reaction system could afford different product classes only by changing the reaction conditions.

Herein, we reported that allylic epoxides could be obtained in high yields without any additive; Meinwald rearrangement products aldehydes or ketones were afforded when the reaction was catalyzed with a Brønsted acid as the catalyst; and the third product class, homoallylic alcohols, were formed under Lewis acid catalysis (Scheme 1).



Scheme 1. Reactions of α-halo ketones with allylzinc bromide.

In the context of our recent investigation on the reaction of allylzinc bromide (**2**) toward α-bromoacetophenone (**1a**) in THF at room temperature, we found that allylic epoxide (**3a**) was formed in 2 h. The best ratio **1a**/**2** was 1:1.2 (Scheme 2). Under the best optimized conditions, a variety of α-halo ketones are discussed herein and the results are shown in Scheme 3.



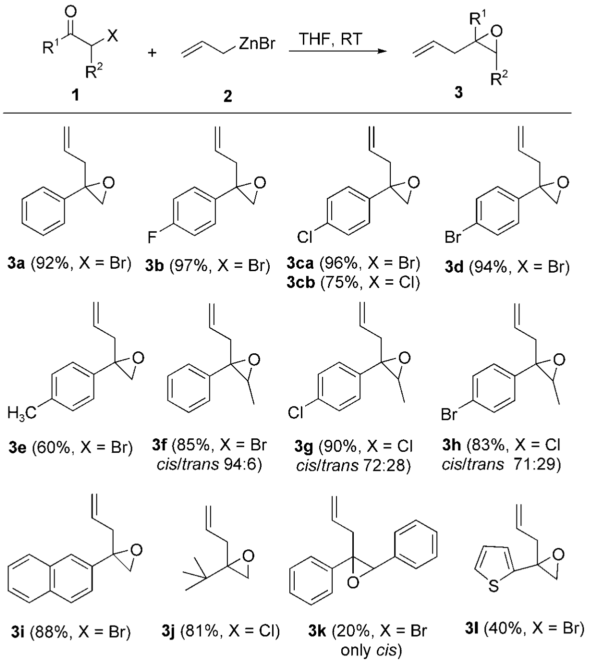
Scheme 2. Reaction of α-bromoacetophenone and allylzinc bromide.

Generally, the α-halo ketones were treated with allylzinc bromide at room temperature in THF and the corresponding allylic epoxides **3a**–**j** were obtained in good yields except for **3e**. We investigated the factors of the electronic effect and steric hindrance at the phenyl- and halo-substituted compounds. Electron-deficient groups at the *para* posi-

---

[a] M. Zhang, Y. Hu, Prof. S. Zhang
Key Laboratory of Organic Synthesis of Jiangsu Province
College of Chemistry, Chemical Engineering and Materials Science
Dushu Lake Campus, Soochow University
Suzhou, 215123 (PR China)
Fax: (+86) 512-65880352
E-mail: zhangsl@suda.edu.cn

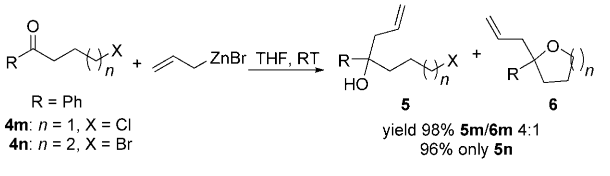
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901487.



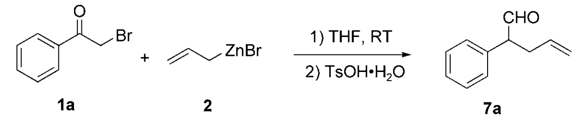
Scheme 3. Products obtained by the allylation of α-halo ketones **1** with allylzinc bromide **2**. Overall isolated yields based on α-halo ketones after silica gel chromatography. The ratio of *cis*/*trans* was given.

tion of phenyl ring were well tolerated in good yields (**3b**, **ca**, **d**), except for **3cb**, which was formed in lower yields because of the lower leaving ability of Cl atom compared with Br. Electron-donating groups at the *para*-position of phenyl ring resulted in relatively diminished efficiency (**3e**). Substrates bearing more sterically hindered groups still yielded the corresponding epoxides (**3f**–**h**) in good yields; the ratio (*cis*/*trans*) was up to 94:6, 72:28, 71:29, respectively. Epoxides **3i** ($R^1 = t$Bu) and **3j** ($R^1 = 2$-thienyl) were also obtained in good yields. When $R^2 = $Ph, **3k** (*cis*) was obtained in lower yield.

We discovered that the addition of allylzinc bromide to ω-halo ketones at room temperature in THF provided a mixture of expected allylic tetrahydrofurans (**6m**) along with non-cyclized products (**5m**) and non-cyclized product **5n** (Scheme 4).



Scheme 4. Reactions of ω-halo ketones and allylzinc bromide.



Scheme 5. Reaction of α-bromoacetophenone and allylzinc bromide catalyzed by $TsOH \cdot H_2O$.

Based on the Meinwald rearrangement, the initial screening showed that α-bromoacetophenone (**1a**) reacted smoothly and economically at room temperature with allylzinc bromide (**2**) in THF catalyzed by 1 equiv $TsOH \cdot H_2O$ affording the aldehyde (**7a**) in good yields (Scheme 5, Table 1). It is worth mentioning that the use of $TsOH \cdot H_2O$ as the catalyst is more advantageous than TfOH both in terms of safety and convenience considerations.

Table 1. Reactions of α-bromoacetophenone and allylzinc bromide catalyzed by acids (by Lewis acids or protic acids).

Entry	Cat.[a]	Cat./Sub.	*t* [h]	Yield [%]
1	$Yb(OTf)_3$	0.1	1	none
2	$InCl_3 \cdot 4H_2O$	0.1	1	none
3	$Mn(OAc)_3 \cdot 2H_2O$	0.1	1	none
4	$BiBr_3$	0.1	20	none
5	$CeCl_3 \cdot 7H_2O$	0.1	20	none
6	HCl	0.1	1	12
7	TfOH	0.1	1	20
8	$TsOH \cdot H_2O$	0.1	1	18
9	$TsOH \cdot H_2O$	0.4	1	60
10	$TsOH \cdot H_2O$	0.8	1	75
11	$TsOH \cdot H_2O$	1.0	1	90
12	$TsOH \cdot H_2O$	1.0	0.67	78

[a] Catalyst and α-halo ketone were added in one portion to the solution of allylzinc bromide (entries 1–5), and catalyst was added to the reaction mixture of α-halo ketone with allylzinc bromide (entries 6–12).

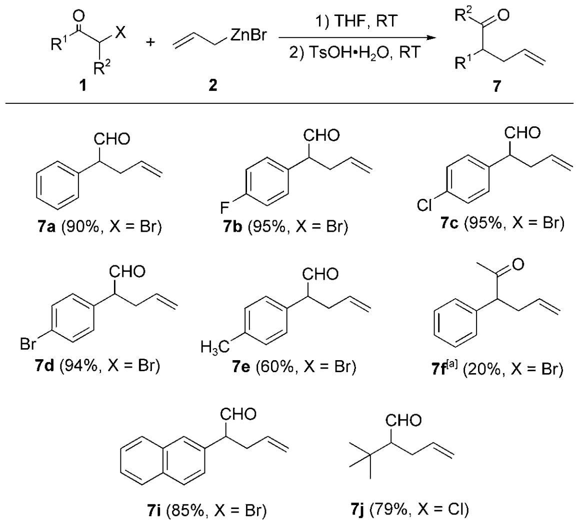
Under the above-optimized conditions, a variety of substrates were investigated and the results were compiled in Scheme 6. We found that aldehydes could be conveniently formed (**7a**–**e**, **7i**, **7j**) from α-halo ketones via the rearrangement of epoxides. The yields of aldehydes were influenced by the formation of the epoxides and consistent with epoxides. When R^2 is CH_3 ketone (**7f**) as Meinwald rearrangement product was obtained in lower yield.

To our surprise, when the reaction catalyst was replaced with Lewis acid, a sterically hindered homoallylic alcohol was obtained in good yield (Scheme 7, Table 2).

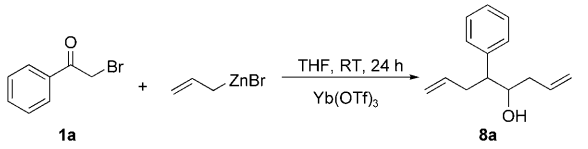
Various α-halo ketones were treated with allylzinc bromide under the best reaction condition and the corresponding homoallylic alcohols were obtained (Scheme 8). The allylation of substrates bearing electron-donating groups was highly efficient (**1e**) in contrast to those bearing electron-deficient groups (**1b**–**d**).

The possible mechanism illustrated in Scheme 9 showed the mutual relations of forming allylic epoxides, aldehydes and homoallylic alcohols.

In summary, we have encountered a novel environmentally benign reaction of allyl bromide with α-halo ketones leading to three different products depending on the different reaction conditions: allylic epoxides were obtained without



Scheme 6. Products obtained by the $TsOH{\cdot}H_2O$-catalyed reaction of α-halo ketones **1** with **2**. Isolated yields based on α-halo ketones. [a] The reaction was carried out at 50 °C.

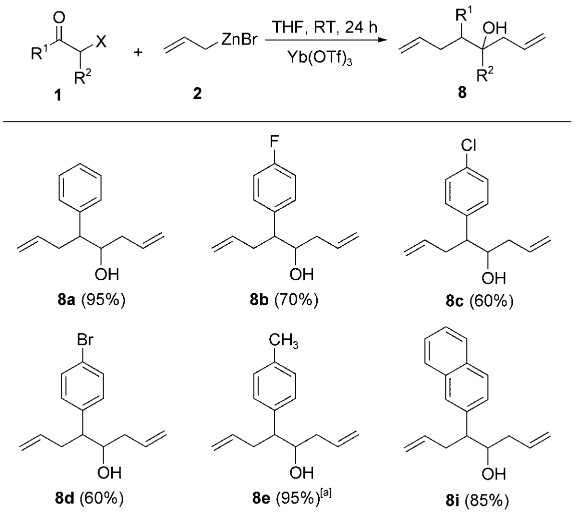


Scheme 7. Reaction of α-bromoacetophenone and allylzinc bromide catalyzed by $Yb(OTf)_3$.

Table 2. Reactions of α-bromoacetophenone and allylzinc bromide catalyzed by Lewis acids.

Entry	Cat.[a]	Cat./Sub.	Yield [%]
1	$InCl_3{\cdot}4H_2O$	0.2	50
2	$CeCl_3{\cdot}7H_2O$	0.2	30
3	$BiBr_3$	0.2	25
4	$Mn(OAc)_3{\cdot}2H_2O$	0.2	50
5	$RuCl_3{\cdot}xH_2O$	0.2	trace
6	$Yb(OTf)_3$	0.2	95
7	$Yb(OTf)_3$	0.15	85

[a] Catalyst and α-halo ketone were added in one portion to the solution of allylzinc bromide.



Scheme 8. Products obtained by the $Yb(OTf)_3$-catalyed reaction of α-bromo ketones **1** with **2**. Isolated yields based on α-bromo ketones. [a] The reaction was completed within 5 h.

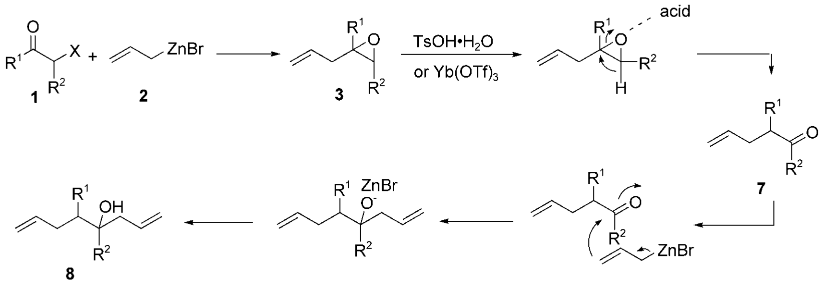
Experimental Section

General procedure for the synthesis of epoxides 3: Allyl bromide (51 μL, 0.6 mmol) and zinc power (0.04875 g, 0.75 mmol) in dry THF (3 mL) under a nitrogen atmosphere at room temperature. The mixture was stirred for about 15 min, and zinc power was disappeared. The stirring was continued to 1 h. Then the solution (3 mL) of substrate (α-halo ketones, 0.5 mmol) was added (the reaction was monitored by TLC). The reaction mixture was stirred for 2 h and then was quenched with water. The resulting mixture was extracted with diethyl ether (3 × 10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed by evaporation under reduced pressure. Purification by column chromatography on silica gel afforded epoxides **3** (300–400 mesh, petroleum ether and ethyl acetate).

Acknowledgements

We thank the Program for Hi-Tech Research of Jiangsu Science and Technology Department (BE2008063), Innovation Fund for Small Technology-based Firms (08C26223201851), Innovator Fund of Suzhou Government (ZXJ0726), Suzhou LAC Co., Ltd., and Suzhou Chiral Chemistry Co., Ltd. (www.suzhoulac.com) for financial support.

any additive and the addition of $TsOH{\cdot}H_2O$ or $Yb(OTf)_3$ as catalyst afforded aldehydes or homoallylic alcohols, respectively. The different products were thus obtained in one reaction, under mild experimental conditions, high yields and a one-pot procedure. Further investigations using other organozinc reagents are currently in progress.



Scheme 9. Mechanism of the reaction of α-halo ketones and allylzinc bromide.

Keywords: allylation · allylzinc bromide · epoxides · ketones · selectivity

---

[1] a) C. Gunanathan, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2009**, *131*, 3146; b) L. C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266; c) V. A. Chebanov, V. E. Saraev, S. M. Desenko, V. N. Chernenko, I. V. Knyazeva, U. Groth, T. N. Glasnov, C. O. Kappe, *J. Org. Chem.* **2008**, *73*, 5110; d) V. Nair, N. Abhilash, P. B. Beneesh, E. Suresh, *Org. Lett.* **2005**, *7*, 4625; e) L. Bagnell, T. Cablewski, C. R. Strauss, R. W. Trainor, *J. Org. Chem.* **1996**, *61*, 7355; f) M. Sánchez-Roselló, A. L. A. Puchlopek, A. J. Morgan, S. J. Miller, *J. Org. Chem.* **2008**, *73*, 1774; g) C. C. Lee, Y. C. Lin, Y. H. Liu, Y. Wang, *Organometallics* **2005**, *24*, 136.

[2] a) O. A. Wong, Y. Shi, *Chem. Rev.* **2008**, *108*, 3958; b) P. Besse, H. Veschambre, *Tetrahedron* **1994**, *50*, 8885.

[3] a) E. N. Jacobsen, M. H. Wu in *Comprehensive Asymmetric Catalysis II* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**; Chapter 18, p. 649; b) B. C. Ranu, U. Jana, *J. Org. Chem.* **1998**, *63*, 8212; c) I. Karamé, M. L. Tommasino, M. Lemaire, *Tetrahedron Lett.* **2003**, *44*, 7687–7689; d) M. W. C. Robinson, K. S. Pillinger, A. E. Graham, *Tetrahedron Lett.* **2006**, *47*, 5919–5921.

[4] J. Meinwald, S. S. Labana, M. S. Chadha, *J. Am. Chem. Soc.* **1963**, *85*, 582.

[5] P. Knochel, P. Jones, *Organozinc Reagents: A Practical Approach*, Oxford University Press, New York, **1999**.

[6] a) L. Stahl, I. P. Smoliakova in *Comprehensive Organometallic Chemistry III*, Elsevier, Amsterdam, **2007**, Chapter 2.06, pp. 309–418; b) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.

[7] a) M. Kosugi, H. Arai, A. Yoshino, T. Migita, *Chem. Lett.* **1978**, 795; b) I. Pri-Bar, P. S. Pearlman, J. K. Stille, *J. Org. Chem.* **1983**, *48*, 4629; c) K. Yano, Y. Hatta, A. Baba, *Synthesis* **1992**, 693–696; d) I. Shibata, S. Fukuoka, A. Baba, *Chem. Lett.* **1998**, 533–534.

[8] J. A. Shin, K. II Choi, A. N. Pae, H. Y. Koh, H. Y. Kang, Y. S. Cho, *J. Chem. Soc. Perkin Trans. 1* **2001**, 946–948.

Received: June 3, 2009