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# Novel Approach to Multifunctionalized Homoallylic Alcohols via Regioselective Ring Opening of Aryl Oxiranes with 3-Iodo Allenoates

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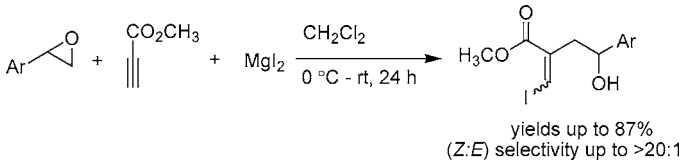
## ABSTRACT




**3-Iodo allenoates were generated in situ and utilized, for the first time, in the ring opening of oxiranes in a regioselective fashion. This simple one-pot three-component reaction protocol provides easy access to highly functionalized homoallylic alcohols in good yields and moderate to very good (*Z*/*E*) selectivity. The two functional groups (ester and halogen) can be further subjected to many synthetic transformations.**

Homoallylic alcohols are valuable building blocks for the synthesis of complex natural products and biologically active compounds.[1,2] These versatile precursors can be used for a variety of important reactions such as Prins cyclization reactions,[3] cycloaddition reactions with nitrile oxides,[4] epoxidations,[2a,5] and aziridinations.[6] Over the past several decades, there have been numerous methods reported for the synthesis of homoallylic alcohols.[7] Most have involved either the allylation of carbonyl compounds or carbonyl-ene reactions. Obviously, the introduction of an additional functionality onto these homoallylic alcohols could greatly enhance their versatility and increase their utility for target-oriented synthesis. Unfortunately, there have been very few methods for the selective synthesis of multifunctionalized homoallylic alcohols reported so far.[8] Very recently, Loh et al. reported an interesting tandem allyl transfer/olefin cross-metathesis reaction for the enantioselective synthesis of homoallylic alcohols having an ester group at C-4. This method gives moderate yields in the case of aliphatic aldehydes but fails with aromatic aldehydes.[9]

From the works of Kishi,[10] Lu,[11] and our group,[12] it is now well established that catalyst systems such as $TiCl_4$/$(n\text{-}Bu)_4NI$, trimethylsilyl iodide (TMSI), $Et_2AlI$, and $MgI_2$ can effectively transfer an iodide anion to α,β-acetylenic ketones/esters to give 3-iodo allenolates/3-iodo allenoates. These 3-iodo allenoates can be reacted with electrophiles such as aldehydes and imines to afford β-iodo Morita−

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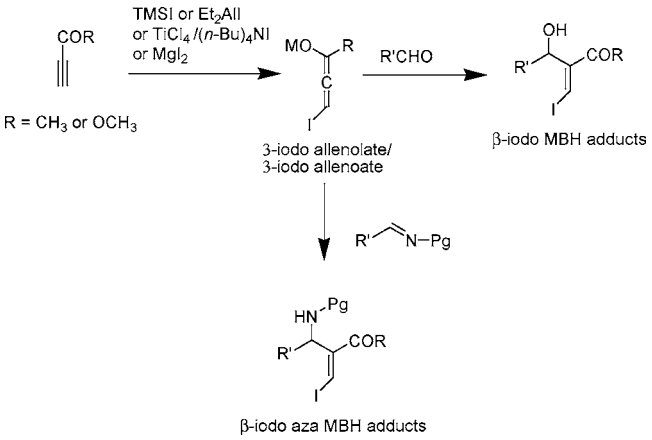
**Scheme 1**

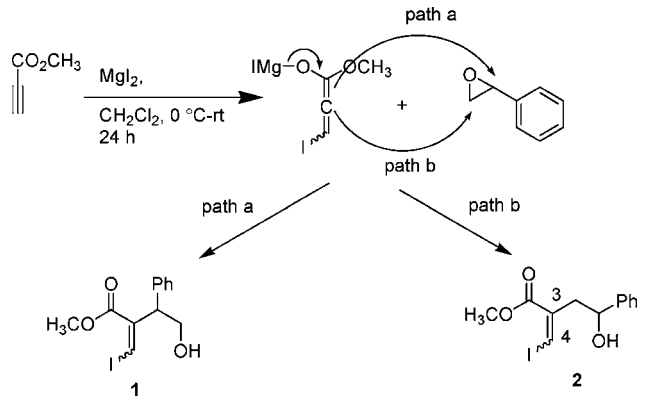



Baylis−Hillman (MBH) adducts and $\beta$-iodo aza-Morita−Baylis−Hillman adducts, respectively (Scheme 1).[12]

We envisaged that such a reaction of 3-iodo allenoates with oxiranes as electrophilic partners would result in homoallylic alcohols with ester and iodo groups on the 3- and 4-positions, respectively. We herein report our preliminary results on the reaction of 3-iodo allenoates with aryl oxiranes to give functionalized homoallylic alcohols. To the best of our knowledge, this is the first example of the synthesis of 3,4-difunctionalized homoallylic alcohols.

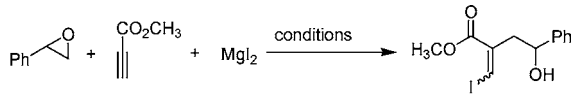
Initial attempts to open the phenyl oxirane ring with in situ-generated 3-iodo allenoate derived from $Et_2AlI$ as a Lewis acid and also as the iodide anion source were unfruitful. No appreciable conversion was observed even after 24 h at room temperature. We next utilized TMSI to replace $Et_2AlI$ for the generation of the 3-iodo trimethylsilyl allenoate for the phenyl oxirane ring opening; no product was observed at all. Fortunately, when we switched to $MgI_2$ as the Lewis acid/iodide anion source for the tandem $\alpha,\beta$-unsaturated addition/ring opening, a 57% yield of the product was obtained after stirring at 0 °C for 24 h. The yield was later improved to 69% when the methyl propiolate/$MgI_2$ combination was used in excess.

**Scheme 2**




On the basis of previous ring openings, it was anticipated that the 3-iodo allenoate could attack phenyl oxirane both at its benzylic carbon (path a, Scheme 2) and at its terminal carbon (path b, Scheme 2) leading to the regioisomers **1** and **2**. It was also found that the chemical yields and regioselectivity of the oxirane ring opening depend on the reaction media, the solvent, and the temperature. The reaction was performed at both 0 °C and room temperature in various solvents. The results are summarized in Table 1.

**Table 1.** Effects of Solvent and Temperature on the Ring-Opening Reaction




0.75 mmol 1.0 mmol 1.0 mmol

| entry | solvent | temp | time (h) | (*Z*/*E*)[a] | % yield |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 0 °C | 24 | 4:1 | 69 |
| 2 | $CH_2Cl_2$ | rt | 24 | 4:1 | 78 |
| 3 | THF | rt | 36 | ND | 23 |
| 4 | $CH_3CN$ | rt | 36 | 5:1 | 48 |
| 5 | toluene | rt | 36 | | 0 |
| 6 | $Et_2O$ | rt | 36 | 2:1 | 34 |
| 7[b] | methanol | rt | 24 | | 0 |

[a] (*Z*/*E*) selectivity was estimated on the basis of $^1$H NMR analysis of crude products. ND = not determined. [b] Methanolysis of phenyl oxirane was observed.

Interestingly, in the present study, $^1$H NMR analysis of the crude product showed that oxirane ring opening occurred predominantly at the less-hindered terminal carbon (path b) of phenyl oxirane leading to the formation of 3,4-disubstituted homoallylic alcohol **2**, although the reaction was performed under Lewis acid conditions. The resulting *Z*,*E* isomers of **2** could be easily separated by $SiO_2$ flash column chromatography.

The (*Z*:*E*) stereochemistry was unambiguously determined by NOESY spectral analysis. The 2D NOESY spectrum (500 MHz; $CDCl_3$) of the major isomer of **2** showed strong correlations between vinylic protons and methylene protons on C-2 and with the methine proton on C-1, whereas in the 2D NOESY spectrum of the minor isomer, no correlations between vinylic protons and other protons were observed (Figure 1).

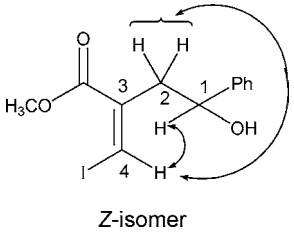
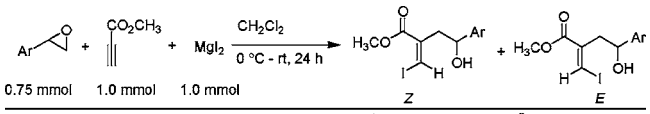
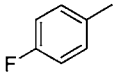
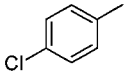
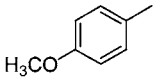
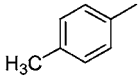
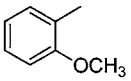
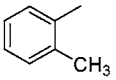
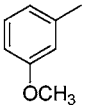



**Figure 1.** NOE correlations in (*Z*)-**2**.

**Table 2.** Results of the Ring Opening of Aryl Oxiranes with 3-Iodo Allenoates




| entry | Ar | Product | (*Z*:*E*)[a] | % yield[b,c] |
|---|---|---|---|---|
| 1 |  | **2a** | 4:1 | 78 |
| 2 |  | **2b** | 5:1 | 87 |
| 3 |  | **2c** | 5:1 | 81 |
| 4 |  | **2d** | 5:1 | 74 |
| 5 |  | **2e** | 5:1 | 74 |
| 6 |  | **2f** | 10:1 | 76 |
| 7 |  | **2g** | >20:1 | 68[d] |
| 8 |  | **2h** | 9:1 | 72 |
| 9 |  | **2i** | 5:1 | 69 |
| 10 |  | **2j** | 4:1 | 73 |

[a] (*Z*/*E*) selectivities were estimated on the basis of $^1$H NMR analysis of crude products. [b] Combined yields of *Z*,*E* isomers. [c] Purified yields after column chromatography. [d] Yield of *Z*-isomer.

As revealed in Table 1, the yield improved significantly when the temperature was raised to room temperature from 0 °C without affecting the (*Z*/*E*) selectivity (entries 1 and 2, Table 1). Methylene chloride was found to be the best solvent for this reaction, giving the highest yields, with only a slight decrease in (*Z*/*E*) selectivity (entries 2 and 4).

The optimal reaction conditions are as follows. In a dry reaction vial filled with $N_2$ is added 1.0 mmol of $MgI_2$ and 3.0 mL of dry methylene chloride. The vial is cooled to 0 °C, and 1.0 mmol of methyl propiolate is added. After stirring for 2 h at this temperature, 0.75 mmol of aryl oxirane, present in 1.0 mL of methylene chloride, is added to the resulting mixture. Stirring is continued at 0 °C for 12 h, and then the temperature is raised to room temperature and stirred for another 12 h.

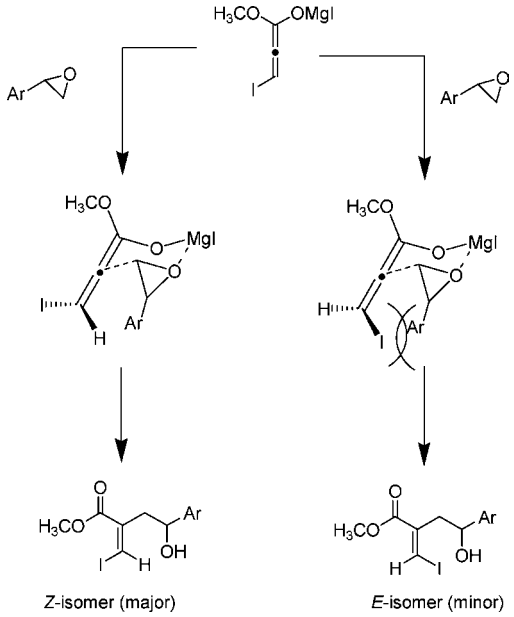
Ten different aryl oxiranes[13] were subjected to the aforementioned ring opening under the above optimized reaction conditions. The results are summarized in Table 2. Both electron-withdrawing groups (entries 2, 3, and 6) and electron-donating groups (entries 4, 5, 7, 8, and 10) on the aromatic system give good results in this reaction, although the yields are slightly higher with those substrates where the oxirane is attached to electron-withdrawing groups. As can be seen from Table 2, the (*Z*/*E*) selectivity was found to vary significantly with the position of substituents on the phenyl ring (compare entries 3, 4, and 5 with 6, 7, and 8).

When a (2-chloro)phenyl substituent was employed (entry 6), the selectivity increased to 10:1 (compare with entry 3). The maximum (*Z*/*E*) selectivity of >20:1 was achieved with the (2-methoxy)phenyl substituent (entry 7). However, the yields were slightly lower with ortho-substituted aryl oxiranes (entries 6−8). Meta substitution on the phenyl ring did not have an obvious effect on (*Z*/*E*) selectivity in the product (entry 10).

Another noteworthy point is that the reaction gave satisfactory results with a heteroaryl oxirane (entry 9).

To explain the observed (*Z*/*E*) selectivity, a closed transition-state model, similar to the one proposed by Kishi,[10b] is shown in Scheme 3. This model is supported by the observation that ortho substitution greatly enhances the (*Z*/*E*) selectivity.

**Scheme 3.** Proposed Transition-State Model




In conclusion, a new simple one-pot three-component reaction protocol that involves tandem I−C/C−C bond

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formation has been developed for the synthesis of 3,4-difunctionalized homoallylic alcohols. Various substituted aryl oxiranes were utilized, and good yields were obtained in all cases. This method is currently being extended to aliphatic and other 1,2-disubstituted oxiranes in our laboratories. Considering the importance of homoallylic alcohols as versatile building blocks, the ester and iodo functionalities at the 3- and 4-positions will become a new tool for the total synthesis of natural products.

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**Supporting Information Available:** Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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