ChemPubSoc Europe

DOI: 10.1002/chem.201304384

CHEMISTRY
A European Journal
Full Paper

Boron Enolates

# An Examination of the Scope and Stereochemistry of the Ireland–Claisen Rearrangement of Boron Ketene Acetals

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**Abstract:** The Ireland–Claisen rearrangement of boron ketene acetals is described. The boron ketene acetal intermediates are formed through a soft enolization that obviates the use of strong bases and the intermediacy of alkali metal enolates. Yields and diastereoselectivities of these rearrangements are very sensitive to the choice of boron reagent, even among those that have been shown to effect quantitative formation of boron ketene acetals from esters. The rearrangement occurs at room temperature for all substrates with generally high levels of stereoselectivity. In contrast to previous reports using boron triflates, the use of a commercially available boron iodide reagent allows for a wider substrate scope that extends to propionates and arylacetates, as well as the previously described α-oxygenated esters. This work also provides insight into the dynamic nature of boron ketene acetals and the ramifications of this behavior for reactions in which they are intermediates.

## Introduction

The Ireland–Claisen rearrangement is a transformation of fundamental importance in organic synthesis.[1,2] It has been used in numerous total syntheses, oftentimes as a key step.[3] Its power stems both from its generality and its predictable stereoselectivity, a consequence of its preference for proceeding through a chairlike transition state. The initially developed method of conducting the rearrangement involves enolization of the ester substrate with a strong base, such as lithium diisopropylamide (LDA), followed by trapping with a silyl chloride to give a silyl ketene acetal. The latter is then heated without isolation to effect rearrangement. Later efforts have explored alternative methods of generating silyl ketene acetals.[4] Although a limited body of work emerged in the early 1990s demonstrating the viability of phosphorus[5] and boron[6,7] ketene acetals in this rearrangement, the majority of reports has continued to focus on silicon. Alternative protocols for conducting this rearrangement may have unique attractive attributes, and the low required temperatures and high stereoselectivity observed in the rearrangements using boron especially piqued our interest. With this motivation in mind, we set to further explore the Ireland–Claisen rearrangement of boron ketene acetals. Through our studies, we have found that the soft enolization reagent combination of dicyclohexyliodoborane ($c$Hx$_2$BI)·Et$_3$N is decidedly effective at promoting this rearrangement, and an array of allylic esters can be converted to γ,δ-unsaturated acids in good yields and excellent diastereoselectivities. We also demonstrate a detailed analysis of the transformation, illustrating important structural considerations that can govern this process.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304384.

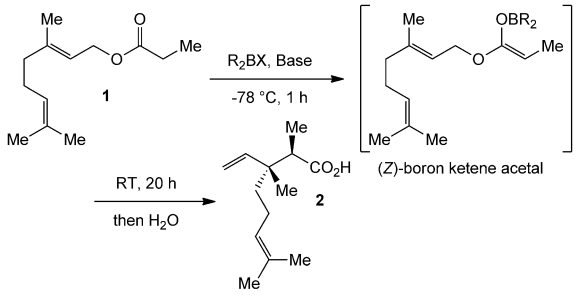
## Results and Discussion

Although many amine-boron Lewis acid pairs are known to generate boron enolates from ketones, few of these are able to form boron ketene acetals from esters.[8] To undergo enolization, esters require more reactive boron Lewis acids along with a tertiary amine of intermediate steric demand. Too small amines form tight adducts with the boron reagent, while too hindered ones fail presumably due to their inability to deprotonate the borane–ester complex. With the very reactive boron iodides, there is also the possibility of ester cleavage promoted by the nucleophilic iodide counterion.

Of the reagent pairs we screened for promoting the rearrangement of geranyl propionate (**1**), we found $c$Hx$_2$BI·Et$_3$N was definitively the most efficient (entry 1), producing a 6:1 mixture of diastereomers in 81% yield (Table 1). The major diastereomer is consistent with the intermediacy of the expected (*Z*)-boron ketene acetal (Scheme 1).[9] The relative inefficiency of $c$Hx$_2$BOTf·Et$_3$N and ($c$C$_5$H$_9$)$_2$BOTf·$i$Pr$_2$NEt came as a surprise, since both pairs have been shown to achieve near quantitative enolization of propionate esters (entries 2 and 3).[10,11] The reagents Bu$_2$BOTf and (Ipc)$_2$BOTf (entries 4 and 5) used in Oh's work[6] also gave poor results when applied to geranyl propionate. Here, all reagents gave major products consistent with the rearrangement proceeding through a chairlike transition state from the (*Z*)-boron ketene acetal.

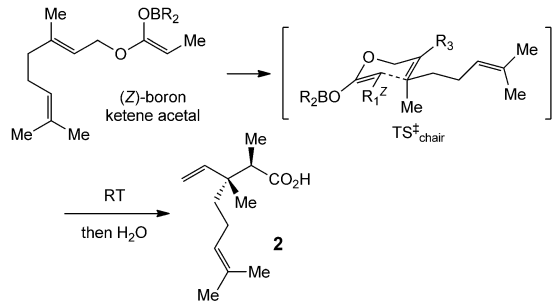
To further optimize the reaction we evaluated a number of other variables. Using an excess of base proved beneficial to stereoselectivity. Triethylamine and diisopropylethylamine worked equally well when used in excess (entries 6 and 7);

**Table 1.** Optimization studies.[a]




| Entry | $R_2BX$ (equiv) | Base (equiv) | Solvent | Yield [%] | d.r. |
|---|---|---|---|---|---|
| 1 | $cHx_2BI$ (1.1) | $Et_3N$ (1.2) | $CH_2Cl_2$ | 81 | 6.0:1 |
| 2 | $cHx_2BOTf$ (2.0) | $Et_3N$ (2.5) | $CH_2Cl_2$ | 52 | 5.3:1 |
| 3 | $(cC_5H_9)_2BOTf$ (2.0) | $iPr_2NEt$ (2.5) | $CH_2Cl_2$ | 44 | 1.9:1 |
| 4 | $Bu_2BOTf$ (1.3) | $Et_3N$ (2.0) | $CH_2Cl_2$ | $<2$ | – |
| 5 | $(Ipc)_2BOTf$ (1.3) | $iPr_2NEt$ (2.0) | $CH_2Cl_2$ | 19 | 1.9:1 |
| ***6*** | ***$cHx_2BI$ (1.1)*** | ***$Et_3N$ (5.0)*** | ***$CH_2Cl_2$*** | ***79*** | ***14:1*** |
| 7 | $cHx_2BI$ (1.1) | $iPr_2NEt$ (5.0) | $CH_2Cl_2$ | 80 | 13:1 |
| 8 | $cHx_2BI$ (1.1) | PIG[b] (1.2) | $CH_2Cl_2$ | 69 | 17:1 |
| 9 | $cHx_2BI$ (1.1) | $Et_3N$ (5.0) | toluene | 62 | 23:1 |
| 10 | $cHx_2BI$ (1.1) | $Et_3N$ (5.0) | $Et_2O$ | 51 | 22:1 |
| 11[c] | $cHx_2BI$ (1.1) | $Et_3N$ (1.03) | $CCl_4$ | 22 | $>49:1$ |
| 12 | $cHx_2BI$ (1.1) | $Et_3N$ (5.0) | hexanes | 55 | 20:1 |
| 13 | $cHx_2BI$ (1.1) | $iPr_2NEt$ (5.0) | $CH_2Cl_2$ | 43[d] | 26:1 |
| 14 | $cHx_2BI$ (1.1) | $Et_3N$ (5.0) | $CH_2Cl_2$ | 68[e] | 12:1 |

[a] Borane was added to a solution of **1**, base, and 4,4′-di-*tert*-butylbiphenyl (internal standard) at $-78\,^{\circ}C$. The resulting solution was stirred 1 h at this temperature then allowed to warm to ambient temperature and stirred 20 h. Yield and d.r. were obtained by $^1H$ NMR analysis of the crude reaction mixture after aqueous workup (no oxidation). [b] PIG: pentaisopropylguanidine. [c] Compound **1** was added to a solution of base and $cHx_2BI$ at $0\,^{\circ}C$ according to Brown's procedure.[8] [d] Rearrangement at $-10\,^{\circ}C$ for 24 h followed by warming to ambient temperature. [e] Rearrangement at $40\,^{\circ}C$.




**Scheme 1.** Stereoselectivity of the rearrangement of geranyl propionate (**1**).

with other bases, including the strongly basic pentaisopropylguanidine (entry 8) used successfully by Corey,[12] the acid was afforded in lower yields. Methylene chloride proved to be the optimal solvent in terms of yield; less polar solvents, like toluene and $CCl_4$, gave higher diastereoselectivity but at the cost of considerable overall efficiency. Like in entries 2 and 3, the conditions in entry 11 were less effective, despite their prior use wherein they afforded quantitative yields of enolization products.[8] Finally, room temperature proved to be the optimal temperature at which to conduct the rearrangement, with both higher and lower temperatures giving lower yields. These reactions suffered mainly from lower conversion, suggesting that boron ketene acetals are slowly quenched[13] in competition with rearrangement. These experiments imply that successful rearrangement requires more than efficient formation of the boron ketene acetal intermediate, as several sets of conditions shown to effect ester enolization in $>95\,\%$ yield fared poorly in our optimization study.

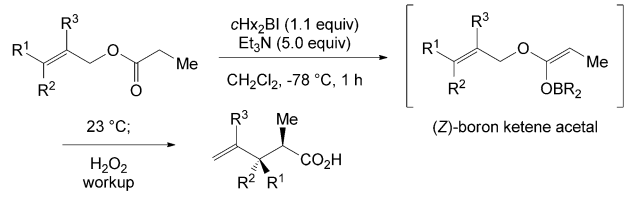
Having found an optimal set of conditions, we examined a range of substrates to probe whether or not the concept of soft enolization could be applied more generally to the Ireland–Claisen rearrangement (Table 2). We were particularly curious as to whether easily ionized (or cleaved) allylic esters would be compatible with the strongly Lewis acidic iodoborane. We were pleased to observe that, under our optimized conditions, even those esters that would be expected to form particularly stable carbocations (e.g., **1**, **7**, and **9**) participated efficiently in the rearrangement. We observed high levels of stereoselectivity, particularly with increased substitution on the alkene. The reason for the lower selectivity for the less-substituted alkene esters is not clear, but it likely stems at least partly from a smaller relative preference for a chairlike transition state over a boatlike one engendered by the low steric demand of the allylic fragment (vide infra).

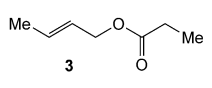
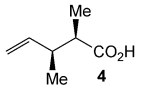
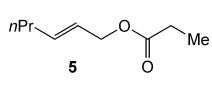
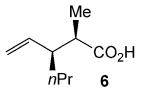
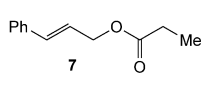
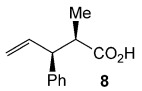
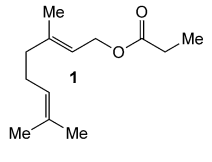
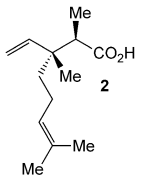
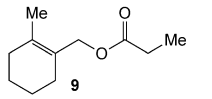
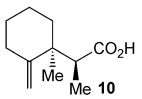
Whereas *n*-alkyl esters rearrange via a (*Z*)-boron ketene acetal arylacetates rearrange via the (*E*)-boron ketene acetal (Table 3). Possibly due to the extended conjugation of the phenyl-substituted boron ketene acetal, these rearrangements are overall faster than those of *n*-alkyl esters, with that of cinnamyl phenylacetate (**11**) done within 10 min at room temperature. We found that toluene was a more effective solvent than methylene chloride in these reactions in terms of stereoselectivity. The rearrangement tolerated a variety of aryl groups, including a protected indole moiety (compound **19**), and all of the rearrangements of arylacetate esters of (*E*)-disubstituted allylic alcohols gave high diastereoselectivity.

Having demonstrated the efficacy of the reaction with simple alkyl esters, we were curious if it could be extended to $\alpha$-alkoxy substituted esters (Table 4). Gratifyingly, these gave comparable yields to our previous substrates along with high stereoselectivities. The major diastereomer in these reactions is consistent with a (*Z*)-boron ketene acetal rearranging through a chairlike transition state. The success of these substrates along with those of the arylacetates shows that alkoxy and nonbasic nitrogen substituents are tolerated in this reaction. Based on all of the above observations, the relative stereochemistry presumably originates via a highly preferred chairlike transition state (Scheme 2).

Having examined the scope of this reaction, we turned our attention to a more detailed analysis of this diastereoselectivity. Because of the nearly perfect stereospecificity of the aldol reaction with boron enolates[8] and the difficulty of directly assaying the *Z*/*E* ratio of boron ketene acetals by NMR spectroscopy, the former is the method of choice in determining the geometric purity of these intermediates. When we subjected

**Table 2.** Rearrangement of propionates via (*Z*)-boron ketene acetals.

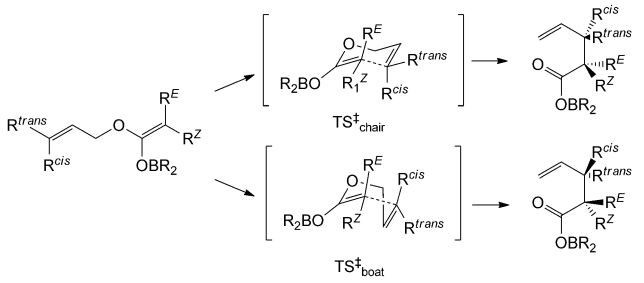



| Entry | Substrate | Product | Time [h] | Yield [%][a] | d.r. (*syn*/*anti*)[b] |
|---|---|---|---|---|---|
| 1 |  **3** |  **4** | 2 | (82)[c] | 83:17 |
| 2 |  **5** |  **6** | 24 | 58 (60) | 83:17 |
| 3 |  **7** |  **8** | 2 | 78 (92) | 83:17 |
| 4 |  **1** |  **2** | 20 | 74 (79) | 93:7 |
| 5 |  **9** |  **10** | 20 | 68 (92) | >98:2 |

[a] Isolated; NMR yields after workup and oxidation of the crude reaction mixture using a suitable internal standard are in parentheses. [b] Diastereoselectivity measured by $^1$H NMR spectroscopy. [c] Not isolated, assayed as the methyl ester.

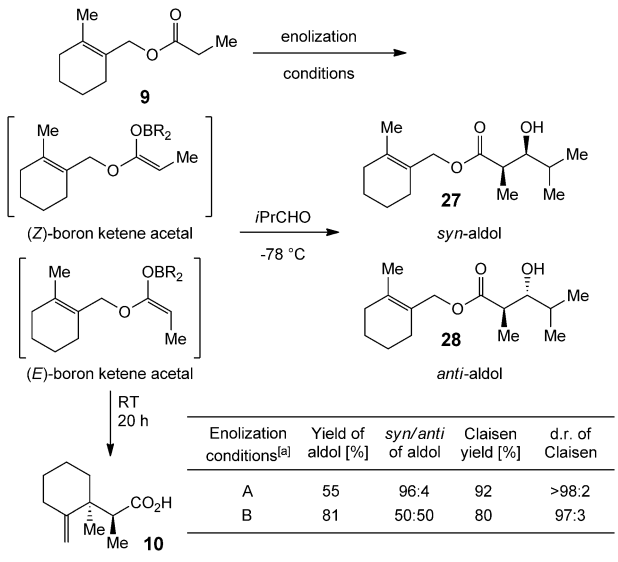
With this result in mind, the rearrangement to give acid **10** (Table 2, entry 5) is somewhat anomalous. This product forms as a >98:2 mixture of diastereomers, a larger ratio than that of the intermediate boron ketene acetals. There are two possible explanations for this outcome (Scheme 3). In scenario A, the (*Z*)-boron ketene acetal could selectively rearrange through a chairlike transition state and the *E* isomer rearrange selectively through a boatlike transition state, converging to the same diastereomeric acid. This behavior has been observed[15] and can serve to relieve substantial nonbonded interactions present in the competing transition state.[16] In this case, however, a boatlike transition state for the rearrangement of the (*E*)-boron ketene acetal of **9** would be significantly hindered due to the fact that it requires the close approach of two methyl groups in an eclipsed butane conformation about the forming bond. This makes it unlikely that preferential rearrangement of the *E* isomer through this alternative transition state topology is the operative process to account for the observed stereoselectivity.

We favor an alternative explanation. The boron ketene acetal intermediate could undergo *Z*/*E* equilibration at the temperature required for the rearrangement with the (*Z*)-boron ketene acetal rearranging much more quickly than the *E* isomer (Scheme 3, scenario B). In this scenario, the reaction operates under Curtin–Hammett type dynamics,[17] requiring that the intermediate undergo *Z*/*E* isomerization. Although this isomerization is generally not considered to occur with silyl ketene acetals under the conditions used to effect rearrangement,[18] such isomeriza-




**Scheme 2.** Stereochemistry of the Ireland–Claisen rearrangement of boron ketene acetals.

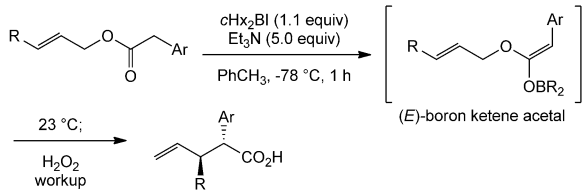
propionate **9** to our standard enolization conditions ($CH_2Cl_2$, −78 °C, 1 h) and trapped the resulting boron ketene acetal with isobutyraldehyde, we observed a 94:6 mixture of *syn*/*anti* aldol products in 55% yield (conditions A),[14] indicating an approximately 94:6 mixture of *Z*/*E* boron ketene acetals (Figure 1). Although the yield of the aldol reaction is low, it is notable that the crude product did not contain any starting material by $^1$H NMR spectroscopy, highly suggestive that enolization was complete in 1 h at −78 °C.

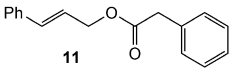
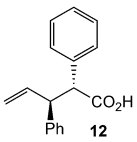
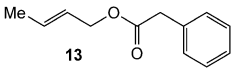
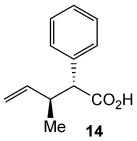
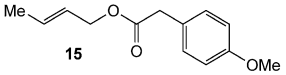
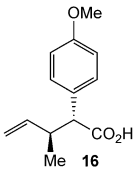
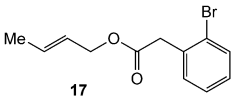
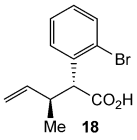
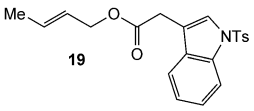
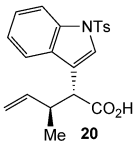



| Enolization conditions[a] | Yield of aldol [%] | *syn*/*anti* of aldol | Claisen yield [%] | d.r. of Claisen |
|---|---|---|---|---|
| A | 55 | 96:4 | 92 | >98:2 |
| B | 81 | 50:50 | 80 | 97:3 |

**Figure 1.** Enolization stereoselectivity via aldol reaction. [a] Enolization conditions: A: *c*$Hx_2BI$ (1.1 equiv), $Et_3N$ (5.0 equiv), $CH_2Cl_2$, −78 °C, 1 h. B: *c*$Hx_2BOTf$ (1.7 equiv), $Et_3N$ (2.5 equiv), $CH_2Cl_2$, −78 °C, 1 h.

**Table 3.** Rearrangement of arylacetates via (*E*)-boron ketene acetals.




| Entry | Substrate | Product | Time | Yield [%][a] | d.r. (*anti/syn*)[b] |
|---|---|---|---|---|---|
| 1 |  **11** |  **12** | 10 min | 83 (89)[c] | 96:4 |
| 2 | | | 10 min | (95)[d] | 91:9 |
| 3 |  **13** |  **14** | 2 h | 79 (80) | 97:3 |
| 4 |  **15** |  **16** | 30 min | 80 (82) | 98:2 |
| 5 |  **17** |  **18** | 45 min | 74 | 93:7 |
| 6 |  **19** |  **20** | 24 h | 84 | 94:6 |

[a] Isolated; NMR yields after workup and oxidation of the crude reaction mixture using a suitable internal standard are in parentheses. [b] Diastereoselectivity measured by $^1$H NMR spectroscopy. [c] Isolated as the methyl ester. [d] Reaction performed in $CH_2Cl_2$.

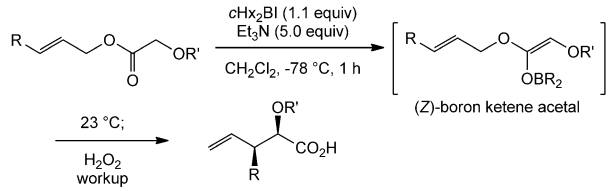
tion has been observed with boron ketene acetals.[19,20] In this case, the product ratio of the reaction is determined by the relative energies of the competing transition states, and the isomeric ratio of the boron ketene acetal intermediate is relatively inconsequential.

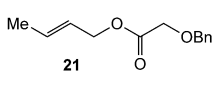
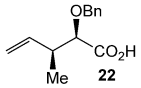
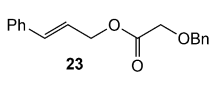
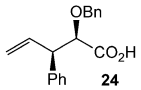
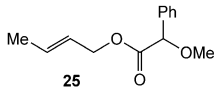
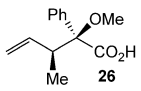
To further probe this issue, we performed a second comparison of aldol and Ireland–Claisen diastereoselectivities (Figure 1, conditions B). With appropriate propionate substrates[21] it is known that *c*Hx$_2$BOTf·Et$_3$N favors the formation of the (*E*)-boron ketene acetal.[10] When we conducted enolization of **9** with this reagent pair followed by trapping with isobutyraldehyde under conditions identical to those above, we obtained a 50:50 mixture of *syn*/*anti* diastereomers of the aldol adduct in a combined NMR yield of 81%. When we allowed the boron ketene acetal formed under these conditions to warm to ambient temperature to effect the rearrangement, we again observed almost complete selectivity for the formation of one diastereomer of **10**, just as we had with *c*Hx$_2$BI. This represents an even more dramatic example of funneling diastereomeric intermediates to one diastereomer of a product and implies that both the isomerization and the rearrangement of the (*Z*)-boron ketene acetal must be faster than the rearrangement of the *E* isomer.[22] The results of these experiments underscore the fact that the diastereoselectivity of the rearrangement is not necessarily dependent on the geometric selectivity of the enolization event.

Scheme 4 illustrates two rearrangements consistent with this explanation. In this case, the phenylacetate ester initially undergoes an *E* selective enolization.[8] When the allylic fragment contains a *cis* olefin, $R^E$ and $R^{cis}$ (Scheme 2) must both be axial in a chairlike transition state. Once again, a boatlike transition state is disfavored due to the close approach of $R^1$ and $R^2$ in this topology. This rearrangement should occur more slowly than one in which the two substituents around the forming bond need not both be axial, and we indeed observe this, with the rearrangement of *cis*-**29** requiring 24 h at room temperature to reach full conversion and that of *trans*-**29** requiring only 45 min. The long reaction time of the former implies that for a *cis* olefin the enolate isomerization is kinetically competitive with the rearrangement.[19] This leads to a significant amount of product being formed through rearrangement of the (*Z*)-boron ketene acetal, which is not initially formed in significant amounts through enolization.

This rationale, however, does not appear to fully explain the fact that propionates rearrange with observed lower stereoselectivity than those with an α-oxygenated group. Both give products with the same relative configuration, but α-oxygenated esters rearrange with approximately tenfold greater selectivity than their α-methyl equivalents. For example, crotyl propionate (**3**) rearranges to give an 83:17 mixture of diastereomers (Table 2, entry 1), whereas crotyl benzyloxyacetate (**21**) rearranges to give a >98:2 mixture (Table 4, entry 1). This difference could be due to the lack of boron ketene acetal isomerization because of complexation to the α-ether moiety, but this alone does not guarantee formation of a single prod-

**Table 4.** Rearrangement of α-alkoxy esters via (*Z*)-boron ketene acetals.




| Entry | Substrate | Product | Time [min] | Yield [%][a] | d.r. (*syn*/*anti*)[b] |
|---|---|---|---|---|---|
| 1 |  **21** |  **22** | 20 | 71 (79) | >98:2 |
| 2 |  **23** |  **24** | 30 | 74 | 98:2 |
| 3 |  **25** |  **26** | 5 | 55 | >98:2 |

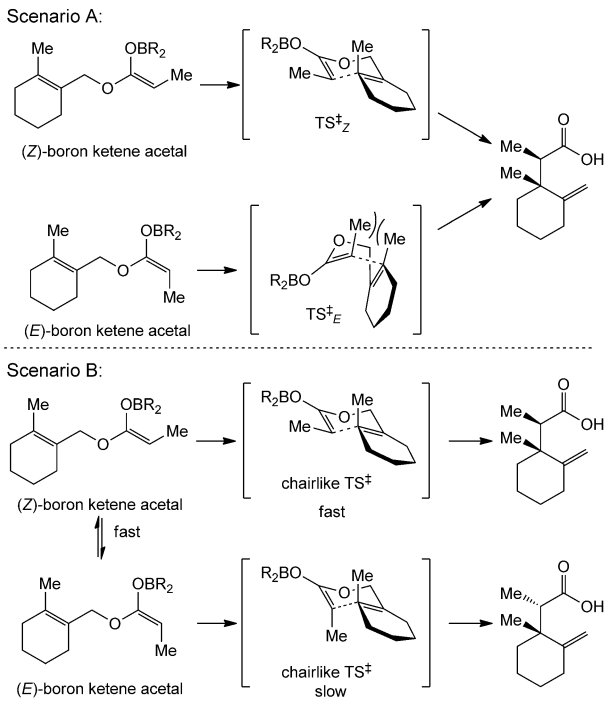
[a] Isolated; NMR yields after workup and oxidation of the crude reaction mixture using a suitable internal standard are in parentheses. [b] Diastereoselectivity measured by $^1$H NMR spectroscopy.

uct diastereomer because of the potential operation of both chair and boat transition states.

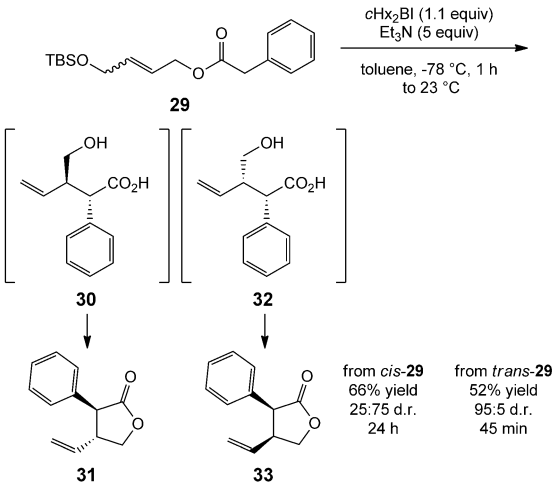
Burke has demonstrated that silyl ketene acetals of *O*-benzylglycolates rearrange to give a 91:9 mixture of diastereomers (Scheme 5).[23] Since the enolization of these esters is controlled geometrically by chelation, this work suggests that silyl ketene acetals of these substrates prefer to rearrange through chair versus boat transition states in an equivalent ratio. The ratios obtained here should be similar in magnitude to those obtained by Burke if the stereoselectivity is governed by a similar chair/boat preference as it is with silyl ketene acetals.[24]

We attribute the observed difference in stereoselectivity between propionates and glycolates to the formation of a boron chelate that changes the steric properties of the boron ketene acetal (Scheme 6). This rigid structure causes a change in boron's geometry from trigonal planar to tetrahedral, locking its alkyl substituents into positions relatively close to the bond-forming centers. This change would not cause a significant increase in nonbonded interactions in the more extended chair transition state but would result in severe steric repulsions between the boron alkyl groups and $R^{trans}$ of the allylic fragment in the more compact boat transition state, disfavoring the latter.

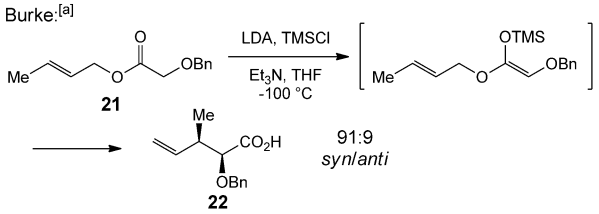
During the course of our optimization studies, we observed some curious results that, while failing to improve upon our best conditions, shed some additional light on the nature of the soft enolization reaction. Abiko and Masamune's work with *c*Hx$_2$BOTf revealed a considerable dependence of the order of addition of base, ester, and borane on



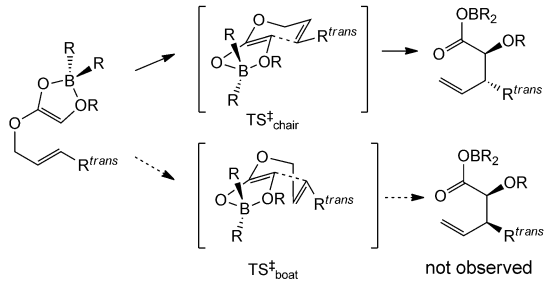

**Scheme 3.** Possible rationales for the diastereoselectivity of the rearrangement to form acid **10**. Scenario A: preferential rearrangements of *Z* isomer through chairlike **TS** and *E* isomer through boatlike **TS**. Scenario B: preferential rearrangement of *Z* isomer of equilibrating *Z*/*E* mixture.




**Scheme 4.** Lactonization of a TBS ether-containing substrate.




**Scheme 5.** Benchmark results for stereoselectivity. [a] Ref. [23].



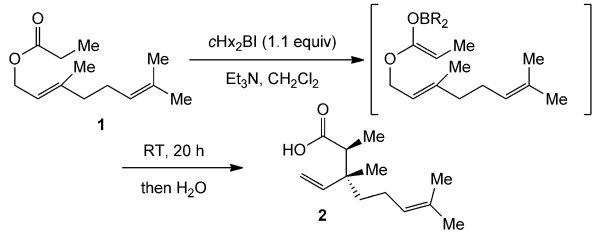

**Scheme 6.** Stereochemistry of the Ireland–Claisen rearrangement of chelate boron ketene acetals.

enolization efficiency.[10] In their case, mixing base and borane prior to addition of the ester substrate led to a time-dependent deactivation of the borane—longer premixing times gave especially poor results. They favored adding borane to a solution of ester and base with $c$Hx$_2$BOTf and base to borane and ester with Bu$_2$BOTf. These respective modes of addition gave >95% yields of boron ketene acetals. These results are in contrast to Ganesan and Brown's experiments using $c$Hx$_2$BI,[8] where most of the work was conducted by mixing equimolar amounts of borane and triethylamine prior to addition of the ester. Using this procedure, they obtained nearly quantitative yields of boron ketene acetals. Thus, each mode of addition of the three reagents had been used successfully in the past.

In our own work, the three possible modes of addition gave very different results (Table 5). Most of the optimization studies (Table 1) were conducted by adding borane last, and this procedure ultimately gave the highest yields (Table 5, entry 1). When borane was premixed with excess base in $CH_2Cl_2$ at 0 °C prior to addition of ester **1** at −78 °C, we obtained low conversion and no detectable product (entry 2). When borane and ester **1** were mixed at −78 °C prior to addition of base (entry 3), we again saw decreased yields along with apparent decomposition products that we had not observed in our best procedure. To further understand this result, we repeated the process in a separate experiment at −40 °C in $CDCl_3$ to allow us to observe the reaction mixture by $^1$H NMR spectroscopy directly. Here, we added $c$Hx$_2$BI to the solution of ester **1** at −40 °C and stirred for 120 s before adding Et$_3$N, and the ester was consumed almost immediately. Upon warming to ambient temperature, we observed geranyl iodide, which had presumably been formed by iodide cleavage of the ester prior to amine addition. It seems that this cleavage reaction is suppressed somewhat at −78 °C but is extremely rapid at −40 °C. It is important to note we obtained very clean crude reaction mixtures using our favored mode of addition, with the sum of product and recovered starting material yields almost always 85–90%, indicating that ester cleavage is not an important side-reaction under these conditions. Apparently, the coexistence of base in the reaction mixture is very important to direct the reaction manifold from cleavage to enolization.

Notably, there were a few classes of substrates that failed to give any detectable rearrangement (Figure 2). Although *n*-alkylacetates, arylacetates, and α-heteroatom-substituted esters rearranged smoothly, isopropylacetates and *tert*-butylacetates failed to rearrange, instead decomposing slowly at slightly elevated temperatures over long reaction times. We believe this is due to increased steric hindrance around the bond-forming centers. Strangely, acetates also failed to rearrange. Abiko, Masamune, and co-workers have shown that acetates are *C*,*O*-diborylated under enolization conditions,[25] and we hypothesize that the α-boryl substituent plays a similar steric role as the branched alkyl groups (Scheme 7). Secondary alcohols appeared to survive the enolization conditions but did not give rearrangement products, even with prolonged heating. These results are noteworthy considering that all of these substrates have been shown to undergo enolization, notwithstanding the anomalous behavior of acetates, and all of these types of silyl ketene acetals do undergo rearrangement.[2]

**Table 5.** Mode of reagent addition.




| Entry | Procedure[a] | $Et_3N$ [equiv] | Conv. [%] | Yield [%][a] | d.r. (*syn*/*anti*)[b] |
|---|---|---|---|---|---|
| 1[b] | A | 5.0 | 90 | 79 | 14:1 |
| 2 | B | 20 | 17 | <2 | – |
| 3 | C | 5.0 | 74 | 45 | 21:1 |

[a] Procedures: A: $c$Hx$_2$BI added to solution of ester **1** and $Et_3N$ at −78 °C and stirred 1 h before warming to ambient temperature and stirring 20 h. B: $c$Hx$_2$BI and $Et_3N$ mixed at 0 °C 5 min before cooling to −78 °C and adding ester **1**. The mixture was then stirred 1 h before warming to ambient temperature and stirring 20 h. C: $c$Hx$_2$BI was added to solution of ester **1** at −78 °C and stirred 5 min before adding $Et_3N$ and stirring 1 h. The mixture was then warmed to ambient temperature and stirred 20 h. [b] Identical to Table 1, entry 6.

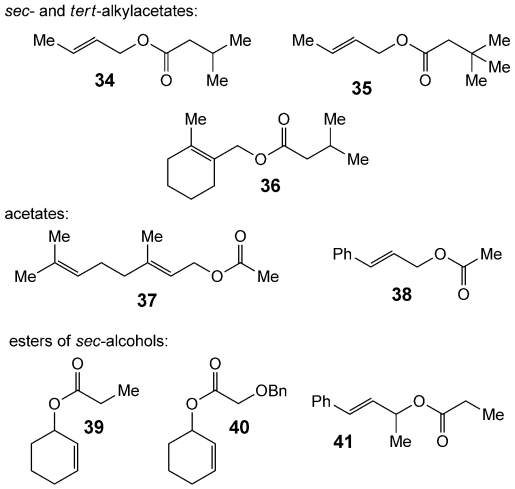
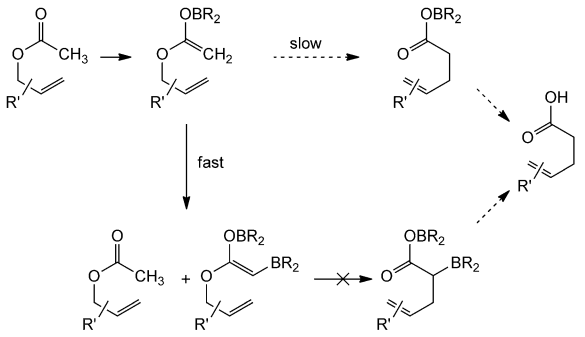



**Figure 2.** Substrates that failed to give rearrangement products.




**Scheme 7.** Rationale for the unreactivity of acetates.

## Conclusion

Overall, our results suggest that the Ireland–Claisen rearrangement of boron ketene acetals holds promise as a synthetically applicable method. The nonbasic nature of the conditions for promoting ketene acetal formation, as well as the generally high levels of observed stereoselectivity, suggest that it should prove to be a viable alternative to existing methods of promoting this useful rearrangement.

## Experimental Section

### Notes on handling *c*$Hx_2BI$

Dicyclohexyliodoborane, the borane reagent used for most of this work, is a very water and oxygen sensitive compound that must at all times be handled and stored under an inert atmosphere. The pure reagent is a clear, colorless liquid at room temperature. Material kept in septum-capped bottles, either neat or in solution, discolors on the order of days to weeks, and strongly colored reagent gives inferior results. After careful experimentation, we found the following protocol to be useful: after synthesis of the reagent by the method of Brown,[8] the crude material was distilled into a Schlenk flask. On completion of the distillation, the product containing flask was stoppered under an Ar purge and immediately evacuated. The flask was taken into an $N_2$ atmosphere glove-box, transferred to a brown glass bottle, and stored at room temperature. Material stored in this way showed no evidence of decomposition after several months had elapsed. The reagent was removed from the glove-box in a syringe as needed and added to a reaction mixture or diluted with hexanes to make a stock solution that was used immediately.

### Notes on workup and removal of boron-containing products

Once the crude reaction mixture is exposed to water, which immediately hydrolyzes the acyloxyborane product, the free carboxylic acid is generally sensitive to iodolactonization, which can occur readily when the iodide containing reaction mixture is exposed to air. Therefore, it is important to quench the reaction mixture with a solution capable of reducing any free $I_2$ to $I^-$. We favored acidic $Na_2SO_3$ for this purpose because the more commonly used $Na_2S_2O_3$ decomposes to insoluble $S_8$ under the acidic conditions necessary for carboxylic acid products to partition into the organic layer.

The removal of boron-containing impurities requires oxidation of the crude reaction mixture with $H_2O_2$. A neutral medium, such as MeOH, at ambient temperature is sufficient for this purpose. The oxidation of the boron-containing byproducts generates 2 equiv cyclohexanol (b.p. 160–161 °C) and an equivalent of boric acid. Boric acid is easily removed by washing with aqueous acid or by directly applying the concentrated reaction product to a silica-gel column. The latter method can also be used to remove cyclohexanol, which can also be removed by heating gently under high vacuum ($<0.1$ torr) for a few minutes. If the oxidation step is not conducted, the borinic acid side-products decompose during chromatography to give boron-containing impurities that tend to co-elute with the desired product.

Methylation of the crude acid product with $CH_2N_2$ requires prior workup and oxidation, along with a final aqueous wash to remove boric acid. The omission of any of these steps gives rise to situations in which even a large excess of $CH_2N_2$ fails to effect methylation to any significant extent. This being said, methylation is not required for efficient purification of these products provided that a small amount of acetic acid is added to the eluent during chromatography.

### Example procedure for optimization experiments using *c*$Hx_2BI$

A solution of geranyl propionate (**1**, 52.6 mg, 0.250 mmol), an internal standard of 4,4′-di-*tert*-butylbiphenyl (8.3 mg, 0.0313 mmol), and the appropriate base in the appropriate solvent was cooled to −78 °C. To this solution was added *c*$Hx_2BI$ (63 μL, 0.275 mmol) dropwise. The solution was stirred at −78 °C for 1 h, allowed to warm to room temperature, and stirred an additional 20 h. The reaction was quenched by being poured into 4:1 sat. aq. $NH_4Cl$/1 M $Na_2SO_3$ (25 mL) then acidified to pH 1 with 2 M aq. HCl. This mixture was extracted with $Et_2O$ (3×10 mL). The combined organic extracts were washed with brine (25 mL), dried with $MgSO_4$, and concentrated. The resulting material was dissolved in $CDCl_3$ (3.0 mL) and analyzed by $^1H$ NMR spectroscopy (300 MHz, 10 s relaxation delay). The NMR spectrum was phase and baseline corrected. The diastereoselectivity of the reaction was determined by the ratio of the integrals of the peak centered at $\delta = 5.87$ (dd, $J = 17.4$, 10.8 Hz, 1H, major diastereomer) and 5.68 ppm (dd, $J = 11.0$, 17.5 Hz, 1H, minor diastereomer). The yield of the reaction was determined by the ratio of the sum of the integrals of these two peaks to the integral of the aromatic protons of 4,4′-di-*tert*-butylbiphenyl at $\delta = 7.52$ (ddd, $J = 8.5$, 2.2, 1.9 Hz, 4H) and 7.44 ppm (ddd, $J = 8.5$, 2.5, 1.7 Hz, 4H).

### General procedure A: rearrangement in $CH_2Cl_2$

To a stirred solution of the starting ester in $CH_2Cl_2$ (0.10 M) was added $Et_3N$ (5 equiv), and the solution was cooled to −78 °C. Neat *c*$Hx_2BI$ (1.1 equiv) was added dropwise, giving a cloudy colorless or pale yellow solution. This solution was stirred at −78 °C for 1 h and then allowed to warm to ambient temperature. The reaction was stirred at room temperature until the starting ester was completely consumed by TLC (eluent typically 19:1 hexanes/ethyl acetate, $KMnO_4$ stain solution) or until the reaction had ceased to progress further, as judged qualitatively by TLC, to a maximum reaction time of 24 h. The reaction was then quenched by being poured into 4:1 sat. $NH_4Cl$/1.0 M $Na_2SO_3$, and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with three portions of $Et_2O$ or EtOAc. The combined organic extracts were then washed with brine, dried with $Na_2SO_4$ and concentrated. The resulting residue was dissolved in MeOH (0.1 M) and

treated with 30% aq. $H_2O_2$ (10 equiv). This mixture was allowed to stand 1 h at room temp, then diluted with EtOH and concentrated to azeotropically remove $H_2O$. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1–2 min to remove most of the cyclohexanol. The crude product was purified by flash column chromatography (usually 19:1 hexanes/EtOAc→89:10:1 hexanes/EtOAc/AcOH eluent) to give the pure product free from cyclohexanol and boron-containing impurities.

### General procedure B: rearrangement in toluene

To a stirred solution of the starting ester in toluene (0.10 M) was added $Et_3N$ (5 equiv), and the solution was cooled to −78 °C. Neat *c*$Hx_2BI$ was diluted with sufficient hexanes to make a 1.0 M solution, and this solution (1.1 equiv) was added dropwise to give a cloudy colorless or pale yellow solution. The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to ambient temperature, during which time a white solid precipitated, then stirred at room temperature until the starting ester was completely consumed as detected by TLC (eluent typically 19:1 hexanes/ethyl acetate, $KMnO_4$ stain solution) or until the reaction had ceased to progress further, as judged qualitatively by TLC, to a maximum reaction time of 24 h. The reaction was then quenched by being poured into 4:1 sat. aq. $NH_4Cl$/1.0 M $Na_2SO_3$, and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with three portions of $Et_2O$ or EtOAc. The combined organic extracts were then washed with brine, dried with $Na_2SO_4$ and concentrated. The resulting residue was dissolved in MeOH (0.1 M) and treated with 30% aq. $H_2O_2$ (10 equiv). This mixture was allowed to stand 1 h at room temperature, then diluted with EtOH and concentrated to azeotropically remove $H_2O$. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1–2 min to remove most of the cyclohexanol. The crude product was purified by flash column chromatography (usually 19:1 hexanes/EtOAc→89:10:1 hexanes/EtOAc/AcOH eluent) to give the pure product free from cyclohexanol and boron-containing impurities.

## Acknowledgements

Colorado State University is acknowledged for support of our program.

**Keywords:** allylic esters · boron · Claisen rearrangement · diastereoselectivity · enolates

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[9] Here we adopt the convention of giving boron the highest priority when assigning the *E*/*Z* geometry of the enolate.

[10] a) A. Abiko, J.-F. Liu, S. Masamune, *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587; b) T. Inoue, J.-F. Liu, D. C. Buske, A. Abiko, *J. Org. Chem.* **2002**, *67*, 5250–5256. c) It should be noted that these systems have been demonstrated to afford the (*Z*)- and (*E*)-boron ketene acetals, respectively, implicating that the geometry was not the sole determinant in the relative inefficiency.

[11] It is possible that the *c*$Hx_2BI$ may also be catalyzing the rearrangement itself. However, varying the quantity of the iodoborane did not improve the overall efficacy of the reaction. For select examples of Lewis acid catalyzed Ireland–Claisen rearrangements of silyl ketene acetals, see: a) G. Koch, P. Janser, G. Kottirsch, E. Romero-Giron, *Tetrahedron Lett.* **2002**, *43*, 4837–4840; b) K. S. Feldman, B. R. Selfridge, *Tetrahedron Lett.* **2012**, *53*, 825–828.

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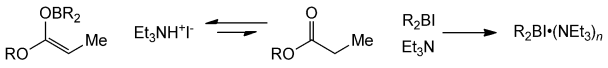
[13] The slow quenching of the boron ketene acetal was observed in $CDCl_3$ when the $^1H$ NMR spectrum of the reaction mixture was recorded directly. This behavior occurred even when the reaction mixture was rigorously protected from atmospheric oxygen and moisture and was unaffected by changes in scale. We hypothesize that the soft enolization reaction is reversible at ambient temperatures and that *c*$Hx_2BI$ generated by this reverse enolization reaction is trapped by excess $Et_3N$, deactivating the borane towards re-enolization of the ester.




[14] The aldol reaction promoted by *c*$Hx_2BI$ proceeded in 55% NMR yield and 38% isolated yield. Because the crude product was clean by NMR and free of obvious aldol decomposition products, we believe the diastereomer ratio of this reaction is indicative of the *Z*/*E* selectivity of the enolization process.

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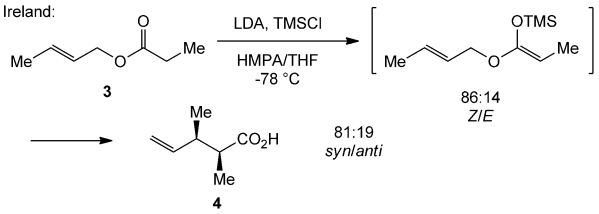


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[20] The presence of *c*$Hx_2BI$ may also facilitate isomerization of the boron ketene acetal.

[21] Although *E*-selectivity is most pronounced in the case of secondary and tertiary propionates, benzyl propionate gives exclusive formation of the (*E*)-boron ketene acetal at −95 °C with *c*$Hx_2BOTf$ and $Et_3N$; see ref. [9b].

[22] It is possible that the conversion of the (*E*)-boron ketene acetal to the product proceeds first through a rate-limiting isomerization to the (*Z*)-boron ketene acetal followed by a fast rearrangement of the *Z* isomer to the product. However, observations of the isomerization occurring at

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Received: November 11, 2013
Revised: December 25, 2013
Published online on March 3, 2014