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Modulating the stereochemical outcome of the Ireland–Claisen reaction of (*E*)- and (*Z*)-allylic glycolates

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ABSTRACT

The diastereoselectivity of Ireland–Claisen rearrangements of allylic glycolates is dependent on the *E*:*Z* ratio of the silyl ketene acetals, the alkene geometry in the allyl unit, and the transition state topography. High yields and excellent diastereoselectivities (>95:5) have been achieved for selected substrates, including those with R_2 = ethyl that results in a newly formed quaternary center. A discussion of the scope, selectivities, and transition state models will be presented.

Introduction

The Ireland–Claisen rearrangement is an important C–C bond forming [3,3] sigmatropic process first described in 1972.[1] Since its introduction, many groups have utilized this transformation both in the construction of natural products[2,3] and in the further methodology development, set forth nicely in numerous reviews.[4–6] Most notably, contiguous stereogenic centers can be formed with high diastereoselectivity. The stereochemical outcome is dictated by the geometries of both the intermediate silyl ketene acetal and allylic alkene, and the transition state topology. While Lewis acids have been shown to promote the Ireland–Claisen reaction with increased diastereoselectivity,[7] no systematic studies have been reported that examine the reactions of α-substituted glycolates under Lewis acid mediation. In addition, all documented examples of Ireland–Claisen reactions of glycolates utilized TMSCl as the silylating agent without investigating possibly superior alternatives.[8] This work focuses on the effects of base, silyl reagent, solvent, and additional α-substitution (resulting in a newly formed quaternary center) on overall yield and diastereoselectivity.

Results and discussion

Unsubstituted benzyloxy glycolates containing an (*E*)-allylic alkene

The effect of Lewis acid mediation on the diastereoselectivity of the Ireland–Claisen rearrangement of α-unsubstituted glycolates (Fig. 1) was examined first. The stereochemical outcome of these transformations with **1a** and **1b** can be rationalized by citing reaction through the canonical chair-like transition state **2** featuring a (*Z*)-silyl ketene acetal. The (*Z*)-silyl ketene acetal geometry presumably results via chelation-controlled[9] enolization of the glycolate. By utilizing TMSCl as the silylating agent and a base/acid workup, easily isolable carboxylic acids were produced without the need for further purification. Very little enhancement in the diastereoselectivity was seen with the addition of catalytic amounts of Lewis acids when using LHMDS as the base (Table 1). For substrate **1a**, $SnCl_4$ appeared to be marginally more effective by both increasing the yield from 94% to near quantitative and the dr from 88% to 94% (Table 1, compare entries 1 and 6).[10] Variation in the outcome of Ireland–Claisen rearrangement for substrate **1b** was a little more pronounced, with an increase in the yield from 83% to 99% by the addition of catalytic $ZnCl_2$ (Table 1, compare entries 9 and 14).

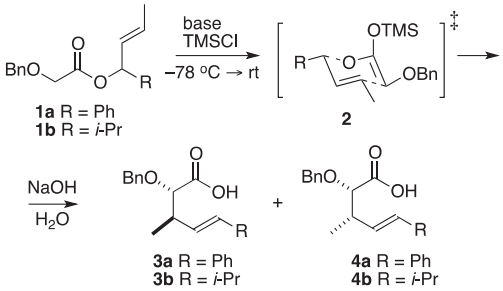

Figure 1. Ireland–Claisen reaction of benzyloxy glycolates **1a** and **1b**.

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Table 1
Lewis acid survey and base comparison with **1a** and **1b** using TMSCl (1.5 equiv) as silylating agent and THF as solvent (emboldened values reflect the best results throughout)

Entry	Subst	Base (1.5 equiv)	Additive (mol %)	Yield (%)	dr[a] (%)
1	**1a**	**LHMDS**	**$SnCl_4$ (2)**	**100**	**94**
2	**1a**	LHMDS	$TiCl_4$ (2)	94	92
3	**1a**	LHMDS	$BF_3{\cdot}OEt_2$ (20)	99	91
4	**1a**	LHMDS	Ti(*i*-OPr)$_4$ (5)	69	93
5	**1a**	LHMDS	$ZnCl_2$ (5)	45	92
6	**1a**	LHMDS	None	94	88
7	**1a**	KHMDS	None	7	>95:5[b]
8	**1a**	NaHMDS	None	—	—
9	**1b**	**LHMDS**	**$ZnCl_2$ (5)**	**99**	**>95:5**[b]
10	**1b**	LHMDS	$SnCl_4$ (2)	93	>95:5[b]
11	**1b**	LHMDS	$BF_3{\cdot}OEt_2$ (20)	92	>95:5[b]
12	**1b**	LHMDS	Ti(*i*-OPr)$_4$ (5)	92	>95:5[b]
13	**1b**	LHMDS	$TiCl_4$ (2)	84	>95:5[b]
14	**1b**	LHMDS	None	83	>95:5[b]
15	**1b**	KHMDS	None	27	84
16	**1b**	NaHMDS	None	—	—

[a] dr = **3a**/**4a** (from **1a**) or **3b**/**4b** (from **1b**) ratio.
[b] ^{1}H NMR detection limit.

The most notable result that emerged from these experiments was the superiority of LHMDS (1.5 equiv vs substrate) as a base for **1a** and **1b** when compared to NaHMDS or KHMDS. The latter two bases at 1.5 equiv vs substrate delivered rearrangement product in only poor yield when they worked at all. It is possible that the kinetics of glycolate deprotonation could play a role in rationalizing these observations.

Increasing the amount of base used in the deprotonation impacted on both the yield and diastereoselectivity of this transform (Table 2). Using 3 equivalents of NaHMDS and KHMDS led to much higher yields of rearrangement products compared to the 1.5 equiv of base as reported in Table 1. In addition, the best diastereoselectivity now was obtained with a sodium counterion for both **1a** and **1b**. Overall, the best conditions for the Ireland–Claisen rearrangement of unsubstituted benzyloxy glycolates **1a** and **1b** utilize 1.5 equiv LHMDS, 1.5 equiv of TMSCl, and catalytic amounts of $SnCl_4$ and $ZnCl_2$, respectively.

Ethyl-substituted benzyloxy glycolates containing an (*E*)-allylic alkene

Lewis acid mediation along with base variation and silylating agent variation was examined for the Ireland–Claisen reaction of the ethyl-substituted benzyloxy glycolates **5a** and **5b** (Fig. 2). These reactions result in the creation of a quaternary stereogenic center with excellent diastereoselectivity, as depicted in **7** and **8**. By going through a transition state featuring a (*Z*)-silyl ketene acetal in a chair conformation, **6**, the phenyl-bearing species **5a** is transformed without Lewis acid present primarily into **7a** in modest yield and with mediocre diastereoselectivity (Table 3, entry 1). Including Lewis acids in the reaction solution did not improve the outcome (Table 3, entries 2–5). Overall, the most notable improvements in yield and diastereoselectivity resulted when the bulkier TIPS group replaced the TMS group (Table 3, entry 7).

However, the addition of select Lewis acids did marginally improve the observed diastereoselectivity with the *i*-Pr-bearing substrate **5b**. When using LHMDS, the diastereoselectivity achieved in going from **5b** to **7b** was increased by the addition of catalytic $SnCl_4$ (Table 3, entry 9). This same level of diastereoselectivity was achieved using KHMDS without the need of a Lewis acid (Table 3, entry 14), with the added benefit of a slight increase in yield. Once again, as with the phenyl-bearing substrate **5a**, the isopropyl-substituted substrate **5b** proceeded to product **7b** with the highest yield and greatest diastereoselectivity when TIPS was used instead

Table 2
Use of increased amounts of base in the Ireland–Claisen rearrangements of **1a** and **1b** using TMSCl (3 equiv) and THF as solvent

Entry	Subst	Base (3 equiv)	Yield (%)	dr[a] (%)
1	**1a**	**NaHMDS**	**64**	**>95:5**[b]
2	**1a**	LHMDS	78	76
3	**1a**	KHMDS	12	60
4	**1b**	**NaHMDS**	**83**	**>95:5**[b]
5	**1b**	LHMDS	80	82
6	**1b**	KHMDS	46	90

[a] dr = **3a**/**4a** (from **1a**) or **3b**/**4b** (from **1b**) ratio.
[b] ^{1}H NMR detection limit.

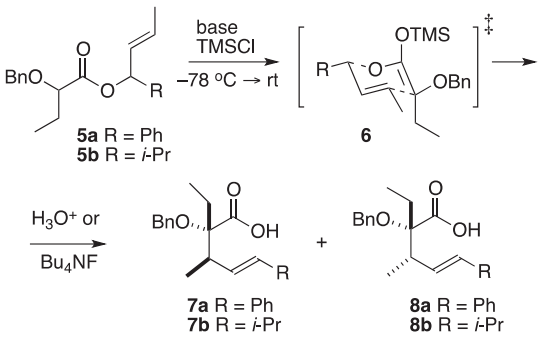

Figure 2. Ireland–Claisen reaction of ethyl-substituted benzyloxy glycolates **5a** and **5b**.

of TMS (Table 3, entry 15). Interestingly, using NaHMDS reversed the diastereoselectivity of the reaction (Table 3, entry 16). It is not clear where the effects of the switch to Na^+ as a counterion are manifest, that is, silyl ketene acetal geometry or the transition stage topography. Overall, the incorporation of an α-ethyl appendage on the substrates **1a** and **1b** neither derailed the Ireland–Claisen rearrangement of the derived species **5a** and **5b** nor diminished the diastereoselectivity attainable, but the chemical yields did suffer a little.

Table 3
Lewis acid survey and base comparison of **5a** and **5b** using TMSCl (1.5 equiv) and THF as solvent

Entry	Subst	Base (1.5 equiv)	Additive (mol %)	Yield (%)	dr[a] (%)
1	**5a**	**LHMDS**	**None**	**48**	**84**
2	**5a**	LHMDS	$TiCl_4$ (2)	36	82
3	**5a**	LHMDS	$SnCl_4$ (2)	44	84
4	**5a**	LHMDS	Ti(*i*-OPr)$_4$ (5)	20	60
5	**5a**	LHMDS	$ZnCl_2$ (5)	13	75
6	**5a**	KHMDS	None	—	—
7[c]	**5a**	KHMDS	None	67	93
8	**5a**	NaHMDS	None	16	65
9	**5b**	**LHMDS**	**$SnCl_4$ (2)**	**43**	**>95:5**[b]
10	**5b**	LHMDS	$TiCl_4$ (2)	34	>95:5[b]
11	**5b**	LHMDS	Ti(*i*-OPr)$_4$ (5)	42	93
12	**5b**	LHMDS	$ZnCl_2$ (5)	47	87
13	**5b**	LHMDS	None	40	88
14	**5b**	**KHMDS**	**None**	**53**	**>95:5**[a]
15[c]	**5b**	**KHMDS**	**None**	**57**	**>95:5**
16	**5b**	**NaHMDS**	**None**	**22**	**59**

[a] dr = **7a**/**8a** (from **5a**) or **7b**/**8b** (from **5b**) ratio.
[b] ^{1}H NMR detection limit.
[c] Entries 7 and 15 utilized TIPSOTf as the silylating agent, 1:1 THF/toluene as the solvent, and a final nBu_4NF treatment to form the acid product.

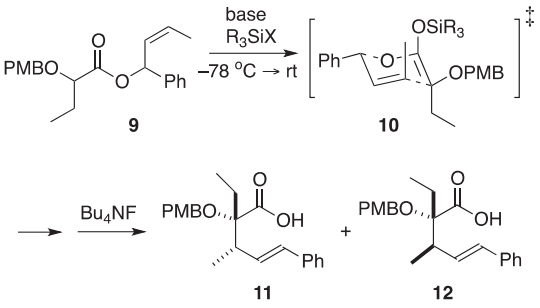

Figure 3. Ireland–Claisen reaction of ethyl substituted PMB glycolate **9** containing a (*Z*)-allylic alkene.

Ethyl substituted (p-methoxy)benzyloxy glycolates containing a (*Z*)-allylic alkene

The diastereoselectivity of the Ireland–Claisen rearrangement for the phenyl-bearing (*Z*)-alkene substrate **9** predictably was reversed compared to the (*E*)-alkene series **5a**/**5b** (Fig. 3). Upon the addition of substrate **9** to a mixture of base and silylating reagent, Ireland–Claisen rearrangement proceeded to furnish the corresponding silyl ester, presumably through a *Z*-silyl ketene acetal in a chair conformation, **10**. Desilylation of this isolable silyl ester afforded carboxylic acid **11** in generally good yield and with high diastereoselectivity over the two-step sequence (Table 4). The use of the PMB ether should impart more flexibility into the tertiary alcohol deprotection chemistry, which may prove valuable in the downstream synthesis projects.

Independent evidence for the (*Z*) configuration of the intermediate silyl ketene acetal can be found through the use of a Claisen-inactive model system **13** (Fig. 4). The derived silyl ketene acetal **14** was isolated and analyzed by ^{1}H NMR nOe experiments. An observed correlation between the PMB CH_2 and the TIPS C–H established the silyl ketene acetal geometry in this species, and by inference the Claisen-active silyl ketene acetals formed from **9**, as (*Z*).

The influence of different silylating reagents on diastereoselectivity was explored with substrate **9** (Table 4). After observing lower yields utilizing TMSCl as the silylating agent for ethyl substituted glycolates (Table 3), the more reactive triflates were examined. Both TIPSOTf and TESOTf greatly increased the yield and diastereoselectivity of the **9** → **11**/**12** conversion (Table 4, entries 1 and 8). These larger silyl ethers may impact on the yield and diastereoselectivity of the rearrangement at several key junctures; (a) their greater electrophilicity (compared to the corresponding chlorides) might promote more rapid enolate trapping, thus minimizing competitive side reactions, (b) the greater steric bulk compared to TMS may make alternative transition states to **10** more energetically penalizing, and (c) the resultant silyl ester products may be more resistant to adventitious cleavage/yield loss compared to the trimethylsilyl alternative. It also should be noted that comparable yields were achieved using TMSCl in the presence of Et_3N, but the diastereoselectivity was a little lower.

A survey of several different bases again was conducted. KHMDS was determined to be the superior base for the transformation of **9** to **11** when using TIPSOTf as the silylating agent. NaHMDS failed to give any product. Furthermore, it was observed that mixing THF with toluene (~1:1 ratio) as the solvent system increased the diastereoselectivity of the reaction.

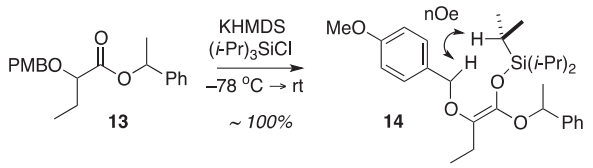

Figure 4. Determination of silyl ketene acetal geometry via nOe analysis.

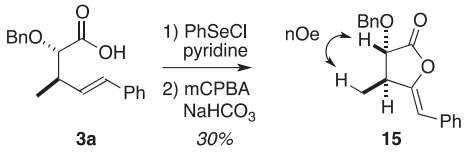

Figure 5. Stereochemical assignment of **3a**.

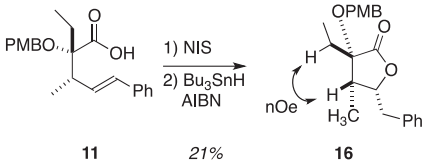

Figure 6. Stereochemical assignment of **11**.

Stereochemical assignments by nOe

Stereochemical assignment of the α-unsubstituted acid **3a** was accomplished by first performing a selenolactonization to give a selenium ether, followed by oxidative elimination within that ether to give **15** (Fig. 5) The stereochemical assignment of **15**, and hence **3a**, follows from nOe analysis. The stereochemical assignment of the major isomer of the isopropyl series, **3b**, was

Table 4
Silylating reagent and solvent effects for transformation of **9** into **11** and **12**, respectively

Entry	Base (3 equiv)	Solvent	Silyl reagent (3 equiv)	Additive (mol %)	Yield (%)	dr[a] (%)
1	**KHMDS**	**Toluene/THF**	**TIPSOTf**	**$TiCl_4$(10)**	**73**	**95**
2	KHMDS	Toluene/THF	TIPSOTf	—	67	>95:5[b]
3	KHMDS	THF	TIPSOTf	—	34	>95:5[b]
4	LHMDS	THF	TIPSOTf	—	50	93
5	NaHMDS	THF	TIPSOTf	—	—	—
6	KHMDS	Toluene	TIPSOTf	—	71	87
7	KHMDS	Toluene	TIPSCl	—	61	75
8	**KHMDS**	**Toluene**	**TESOTf**	—	**75**	**92**
9	KHMDS	Toluene	TMSOTf	—	—	—
10	KHMDS	Toluene	TMSCl	Et_3N	71	87
11	KHMDS	Toluene	TMSCl	—	13	78

[a] dr = **11**/**12** ratio.
[b] ^{1}H NMR detection limit.

inferred by the comparison of its ^{1}H NMR spectral data with those of **3a**.

Stereochemical assignments within the ethyl-substituted series were accomplished by first iodolactonizing the corresponding carboxylic acid **11**, followed by reductive removal of the iodide to give a single compound **16** that was analyzed by ^{1}H NMR nOe (Fig. 6). Similarly, the stereochemical assignments of the major isomer **7a** from the benzyl ether/(*E*)-alkene series were inferred from ^{1}H NMR spectral data comparisons with **11**.

Conclusions

The Ireland–Claisen rearrangement of both (*E*)- and (*Z*)-alkenyl α-ethylglycolates can proceed with high levels of diastereoselectivity, and in excellent yields, under certain experimental conditions. The best results were obtained by using bulkier silylating reagents (e.g., TIPS), potassium hexamethyldisilazide as a base, and in a 1:1 toluene-to-THF solvent system. Catalytic Lewis acid additives did not have significant impact on either the yield or diastereoselectivity of the rearrangement for the systems examined.

Acknowledgment

Financial support from the National Science Foundation (CHE 0956458) is gratefully acknowledged.

Supplementary data

Supplementary data (Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for **1b**, **3a**, **3b**, **5a**, **5b**, **7a**, **7b**, **9**, **11**, **13**, **14**, **15**, and **16**.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.011.

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10. Representative experimental*: 2-Benzyloxy-3-methyl-5-phenyl-pent-4-enoic acid* (**3a**). To a stirring solution of LHMDS (1.0 M in THF, 405 μL, 0.40 mmol) in 2.8 mL of THF at −78 °C was added freshly distilled TMSCl (53 μL, 0.40 mmol) dropwise. A solution of benzyloxy-acetic acid 1-phenyl-but-2-enyl ester (**1a**) (0.080 g, 0.269 mmol) in 200 μL of THF was added dropwise, followed by $SnCl_4$ (1.0 M in CH_2Cl_2, 11 μL, 0.011 mmol). The solution was stirred at −78 °C for 30 min, 0 °C for 30 min, and then warmed to room temperature. After 14 h, 1 M NaOH was added, stirred vigorously for 1 h, and Et_2O was added. The resulting solution was partitioned between Et_2O and 1 M NaOH and the organic layer was extracted with 1 M NaOH. The combined aqueous fractions were acidified with 3 M HCl to pH 3, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2-benzyloxy-3-methyl-5-phenyl-pent-4-enoic acid (**3a**) (0.080 g, 100%, 94% dr) as a colorless oil. IR (thin film) 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.19 (m, 10H), 6.47 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.9, 8.0 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.00 (d, J = 4.7 Hz, 1H), 2.90 (m, 1H), 1.21 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 137.7, 137.5, 131.35, 131.26, 129.0, 128.9, 128.6, 128.5, 127.8, 126.7, 82.0, 73.5, 40.9, 15.7; LRMS (ESI) m/z (relative intensity) 314.2 (100%, M+NH_4^+).