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Three-Component Glycolate Michael Reactions of Enolates, Silyl Glyoxylates, and α,β-Enones

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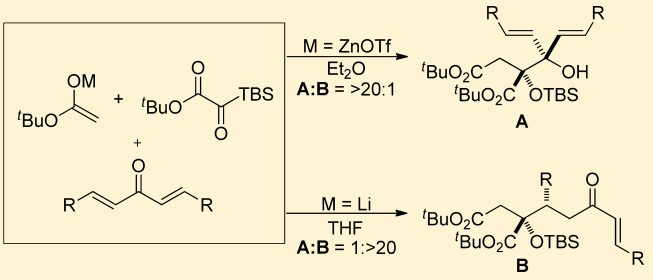
Supporting Information

ABSTRACT: Silyl glyoxylates react with enolates and enones to afford either glycolate aldol or Michael adducts. Product identity is controlled by the countercation associated with the enolate. Reformatsky nucleophiles in the presence of additional $Zn(OTf)_2$ result in aldol coupling (**A**), while lithium enolates provide the Michael coupling (**B**). Deprotonation of the aldol product **A** with LDA induces equilibration to form the minor diastereomer of Michael product **B**. This observation suggests that formation of the major diastereomer of Michael product **B** does not occur via an aldol/retro-aldol/Michael sequence.



INTRODUCTION

Chiral glycolic acids are common subunits of biologically active molecules such as zaragozic acid, trachyspic acid, and echinosporin (Figure 1);[1] therefore, the development of new

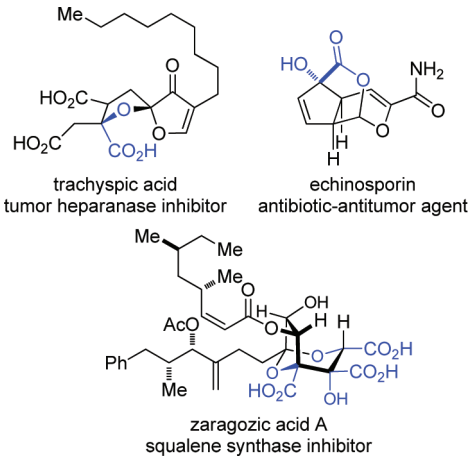
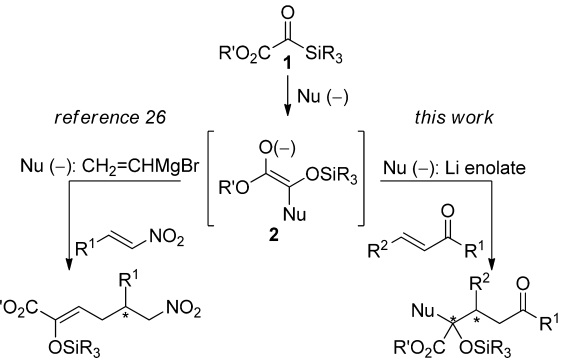


Figure 1. Biologically active δ-oxygenated glycolic acids.

methods that produce α-substituted glycolic acids and esters remains an important goal. Glycolate aldol[2,3]/alkylation[4,5] reactions, nucleophilic additions to α-ketoesters,[6,7] and ester enolate oxygenations[8] are among the most reliable means to generate chiral α-hydroxy esters.[9] On the other hand, syntheses of δ-oxygenated glycolic acid derivatives are most directly achieved via glycolate Michael reactions.[10−18]

Chemical reactions that generate multiple C−C bonds in a single operation are valuable transformations as they provide time- and cost-effective alternatives to multistep routes.[19] Silyl glyoxylate **1** has been utilized in such cascade reactions

Scheme 1. Michael Acceptors as Terminal Electrophiles



(Scheme 1).[20,21] Reagent design hinges on a nucleophile-triggered [1,2]-Brook rearrangement to achieve umpolung reactivity at the silyl ketone carbon.[22] The resulting enolate **2** may then react with various carbonyl electrophiles to provide glycolate aldol[21] or Claisen[23] products. While there are several examples of enolate **2** participating in 1,2-addition with carbonyl[24] or imine[25] electrophiles, reactions with $\pi_{C=C}$ electrophiles have been less studied. To date, only vinylogous trapping of enolate **2** with nitroolefins to provide chiral enolsilanes has been reported.[26] In contrast to nitroolefins, enone electrophiles may exhibit ambident behavior, with both aldol addition and Michael addition pathways possible. Reactions with enone electrophiles would therefore need to be controlled regioselectively. This report describes the development of a three-component glycolate Michael reaction

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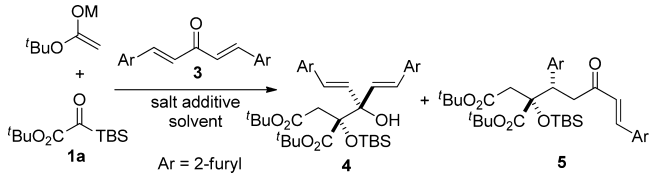
Table 1. Three-Component Coupling: Influence of Counterions



entry	M	salt	solvent	4:5	dr (5)
1	ZnBr		Et_2O	4.2:1.0	ND
2	ZnBr	$ZnCl_2$	Et_2O	1.0:1.2	ND
3	ZnBr	$ZnBr_2$	Et_2O	1.0:1.0	ND
4	**ZnBr**	**$Zn(OTf)_2$**	Et_2O	**>20:1**	
5	Cu		THF	decomp	
6	CuCl		THF	decomp	
7	$TiCl_3$		THF	decomp	
8	K		THF	decomp	
9	Li		Et_2O	1.0:>20	1:1.5
10	Li		THF	1.0:>20	2.1:1
11	**Li**	**LiCl**	**THF**	**1.0:>20**	**3.5:1**

that displays counterion-dependent regioselectivity for 1,4- versus 1,2-addition to α,β-unsaturated ketones.

RESULTS AND DISCUSSION

Preliminary experiments utilized the Reformatsky reagent of *tert*-butyl bromoacetate,[23] TBS-*tert*-butyl silyl glyoxylate,[20] and difurylideneacetone[27] (dfa), which resulted in a mixture of glycolate aldol and Michael three-component coupling products with <75% conversion (Table 1). In an effort to increase conversion by Lewis acid activation of the enone, a number of zinc salts were screened as additives. No significant improvement in conversion was observed, but the ratio of 1,4-addition to 1,2-addition was influenced. While $ZnCl_2$ and $ZnBr_2$ additives provided no selectivity for Michael versus aldol products, zinc triflate produced exclusively the aldol 1,2-addition product **4**. Examples of highly selective 1,2-addition to sterically unbiased α,β-enones by Reformatsky reagents are scarce.[28,29]

Noting the influence of counterion on regioselectivity and aiming to access the complementary glycolate Michael addition products, we tested a series of cationic counterions. After various metal enolates proved ineffective as nucleophilic triggers (entries 5−8, Table 1), lithium enolates provided exclusively the desired 1,4-addition (entries 9−11). The addition of superstoichiometric lithium chloride provided optimal conversion and diastereoselectivity, which may be due to altered aggregation of the glycolate enolate or an increased degree of chelation during Michael addition.[30,31]

Reaction optimization revealed that the order of reagent addition influenced the diastereoselectivity. Addition of silyl glyoxylate to a solution of acetate enolate at −78 °C and warming to 0 °C, followed by addition of the enone, resulted in modest diastereoselection (2.1:1 dr for both dfa and chalcone). However, an increase in diastereoselectivity was observed when the enone and silyl glyoxylate were added simultaneously to a solution of the acetate enolate (3.5:1 dr for dfa, 4.0:1 dr for chalcone). Simultaneous reagent addition is possible due to the lithium enolate nucleophile's high selectivity for the silyl glyoxylate over the enone electrophile, providing the desired three-component coupling products.

Effective enones possessed electron-rich aromatic, electron-poor aromatic, or heteroaromatic substituents. A chiral silyl glyoxylate (R = *trans*-2-phenylcyclohexanol,[32,33] entry 9) underwent three-component coupling with moderate diastereoselectivity (**13**:Σothers = 4.8:1), demonstrating the potential viability of chiral auxiliary-mediated glycolate Michael reactions.

Ineffective Michael acceptors included those with sterically hindered β-positions (R^2 = *t*-Bu or 2-substituted phenyl) and α,β-unsaturated aldehydes, both of which favored three-component 1,2-addition. Enolizable aliphatic enones did undergo the desired three-component coupling but usually suffered from low conversion, probably due to quenching of enolate **2** via proton transfer. α,β-Unsaturated esters and lactones were unreactive terminal electrophiles.

Relative stereochemistry was determined by glycolate Michael addition to enone **14**, followed by elaboration to trachyspic acid trimethyl ester (Scheme 2).[34] Further evidence was obtained by crystallization and X-ray analysis of ketone **7**, which confirmed the *syn*-relationship between 2-furyl and silyl ether substituents (Figure 2).[35,36] The stereochemical result is consistent with (*Z*)-enolate geometry[37] according to Heathcock's model for Michael addition of ester enolates to enones.[38] A closed eight-membered transition state, in which steric interactions between the enolate's *O*-*tert*-butyl group and the enone's phenyl substituent are minimized, may be operative (Figure 3).

The origin of the observed inversion of regioselectivity upon switching from Zn to Li acetate enolates was of interest (Table 1). In general, additions to a C−C double bond are more exergonic than additions to a C−O double bond;[39] therefore, a hypothesis that required evaluation was that the observed selectivity reversal arose from kinetic (1,2-addition) versus thermodynamic (1,4-addition) control. By this rationale, the $Zn(OTf)_2$-mediated reaction would proceed irreversibly to afford the observed aldol product. On the other hand, the Li-mediated reaction would involve an initial aldol addition, followed by retro-aldol fragmentation, and finally 1,4-addition to provide the observed Michael addition product.

To test the proposed retro-aldol/Michael sequence, aldol product **4** was deprotonated with LDA in the presence of LiCl (Scheme 3). The glycolate Michael product was indeed obtained, *but it favored the diastereomeric Michael adduct* **5-*anti*** rather than adduct **5-*syn*** that was obtained in the three-component coupling of the lithium acetate enolate, silyl

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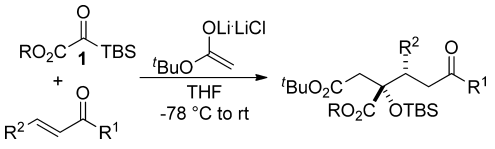
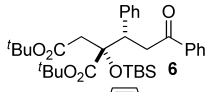
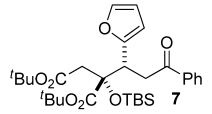
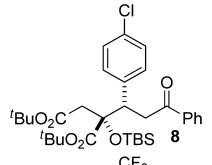
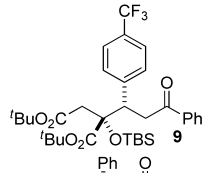
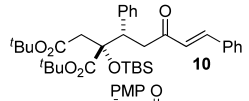
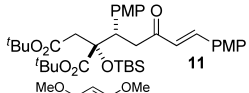
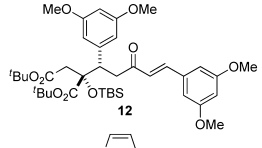
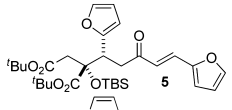
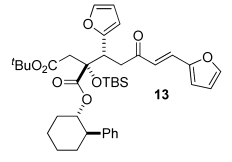
Table 2. Scope of 1,4-Addition[a,b]



entry	product	yield	dr
1		58%	4.0:1
2		63%	4.9:1
3		69%	3.8:1
4		55%	2.7:1
5		42%	2.4:1
6[c]		40%	1.9:1
7		41%	1.6:1
8		50%	3.5:1
9		80%	4.8:1 (**13**:Σ minor)

[a]Reagents: LiCl (8.0 equiv), enolate (1.9 equiv), **1** (2.1 equiv), enone (1.0 equiv). [b]See the Supporting Information for detailed procedures. [c]PMP: 4-methoxy-phenyl.

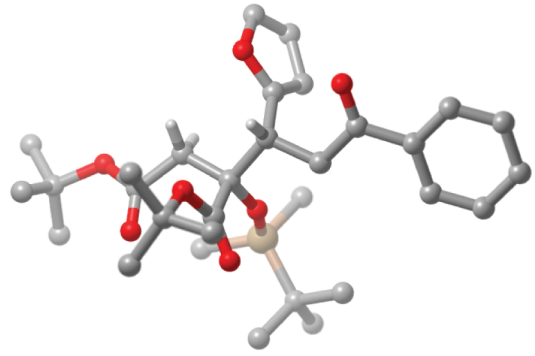


Figure 2. X-ray structure of ketone 7 (some hydrogens have been omitted for clarity).

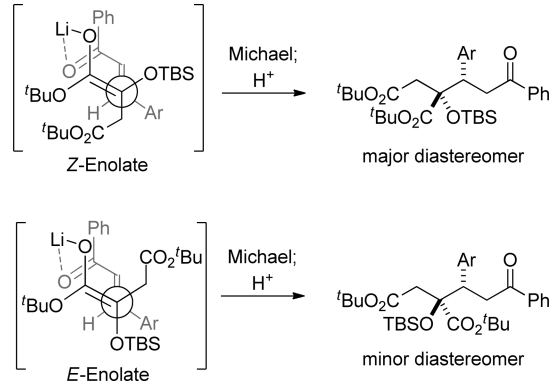
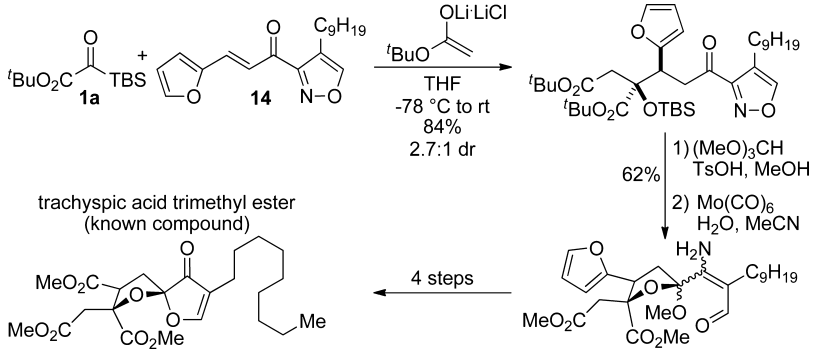


Figure 3. Proposed transition states.

glyoxylate, and dfa. Diastereoselectivity in the addition of ester enolates to enones is believed to stem from enolate geometry.[38] Therefore, retro-aldol fragmentation may provide (*E*)-enolate **2***E*,[40] whereas Brook rearrangement following the addition of lithium acetate enolate to silyl glyoxylate has previously been shown to produce the (*Z*)-enolate **2***Z*.[37]

Since the retro-aldol/Michael sequence provides the opposite diastereomer from the three-component coupling reaction, it is unlikely that the three-component Michael addition products **5**−**13** result from reversible aldol addition followed by Michael addition. To the extent that the aldol/retro-aldol/Michael addition pathway is operative, it likely results in formation of **5**-*anti* and a net erosion of diastereoselectivity in the Michael-terminated Li^+-based three-component couplings.

Scheme 2. Stereochemical Proof



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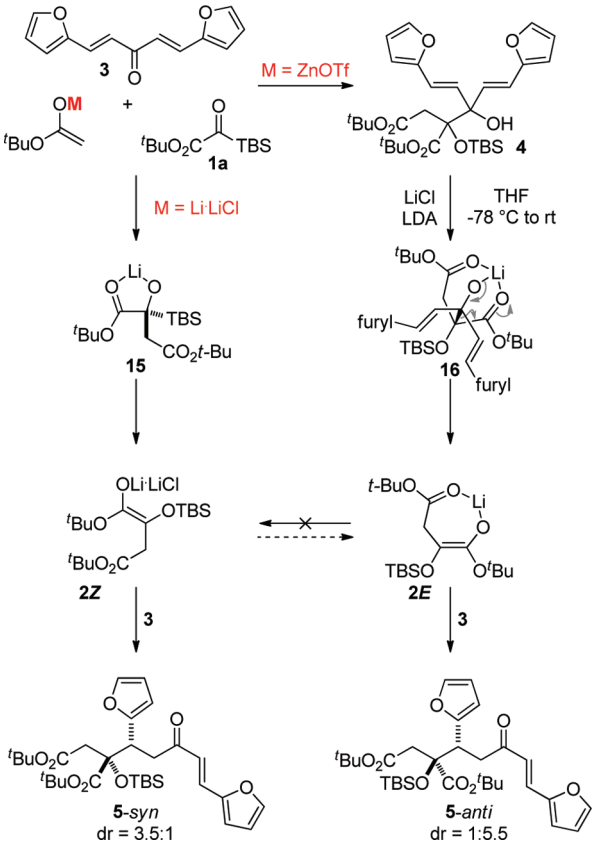
Scheme 3. LDA-Induced Rearrangement of Aldol Product



CONCLUSION

In summary, we have developed a chemoselective and regioselective three-component coupling reaction of lithium enolates, silyl glyoxylates, and α,β-unsaturated ketones. The products possess two contiguous stereogenic centers, including a protected tertiary alcohol, with potential for synthetic elaboration (Scheme 2). The regioselectivity of glycolate enolate addition to the α,β-unsaturated ketone may be switched to favor exclusively aldol addition simply by modifying the counterion.

EXPERIMENTAL SECTION

Di-*tert*-butyl 2-((*tert*-Butyldimethylsilyl)oxy)-2-((1*E*,4*E*)-1,5-di(furan-2-yl)-3-hydroxypenta-1,4-dien-3-yl)succinate (4). To the Reformatsky reagent of *tert*-butyl bromoacetate[23] (0.39 M in Et_2O, 1.5 mL, 0.583 mmol, 2.5 equiv) was added 0.9 mL Et_2O. The solution was cooled to −30 °C, and a solution of *tert*-butyl *tert*-butyldimethylsilyl glyoxylate[20] (142 mg, 0.583 mmol, 2.5 equiv) in Et_2O (1.5 mL) was added. The solution was slowly warmed to 0 °C over 30 min before a solution of $Zn(OTf)_2$ (85 mg, 0.233 mmol, 1.0 equiv) and difurylideneacetone (50 mg, 0.233 mmol, 1.0 equiv) in Et_2O (3.0 mL) was added. (Some $Zn(OTf)_2$ would not dissolve and was not transferred.) The solution was slowly warmed to room temperature over 15 h, and then saturated NH_4Cl (5 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (97:3 to 95:5 petroleum ether/EtOAc gradient) furnished **4** (56 mg, 0.0974 mmol, 42% yield) as a colorless oil. Analytical data for **4**: IR (thin film, cm^{-1}) 3437, 2930, 2856, 1734, 1472, 1394, 1369, 1253, 1013; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 2H), 6.59−6.52 (m, 3H), 6.38−6.33 (m, 3H), 6.21 (t, J = 4.4 Hz, 2H), 3.83 (brs, 1H), 3.17 (d, J = 17.6 Hz, 1H), 2.64 (d, J = 17.6 Hz, 1H), 1.46 (s, 9H), 1.42 (s, 9H), 0.93 (s, 9H), 0.25 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 169.7, 152.9, 142.0, 128.5, 127.6, 118.1, 117.5, 111.2, 108.0 (2 peaks), 83.1, 82.7, 80.6, 78.8, 41.4, 28.1, 27.9, 26.2, 19.0, −2.5, −2.8; TLC (10:90 EtOAc/petroleum ether) R_f 0.50; HRMS (ESI) calculated for $C_{31}H_{46}O_8SiCs$ 707.2016, found 707.2040.

General Procedure A for Aldol/Michael Three-Component Couplings. To a solution of LiCl (8.0 equiv, 1.9 M) in THF was added $^iPr_2NH$ (2.1 equiv). The solution was cooled to 0 °C, and ^{n}BuLi (1.4 M in hexanes, 2.0 equiv) was added. The solution was stirred at 0 °C for 10 min and then stirred at room temperature for 10 min. The solution was cooled to −78 °C, and a solution of ^{t}BuOAc (1.9 equiv) in THF (1.1 M) was added. The solution was stirred at −78 °C for 1 h. A solution of α,β-unsaturated ketone (1.0 equiv, 0.2 M) and *tert*-butyl *tert*-butyldimethylsilyl glyoxylate[20] (2.1 equiv) in THF was added. The solution was allowed to slowly warm to room temperature over 3 h and then stirred at room temperature for 14−24 h. The reaction was diluted with Et_2O (15 mL) and quenched with saturated NH_4Cl (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The resulting oil was purified as indicated.

Di-*tert*-butyl 2-((*tert*-Butyldimethylsilyl)oxy)-2-(3-oxo-1,3-diphenylpropyl)succinate (6). General procedure A was performed using *trans*-chalcone (42 mg, 0.200 mmol, 1.0 equiv). ^1H NMR analysis of the crude mixture revealed a diastereomeric ratio of 4.0:1. Purification by flash chromatography (97:3 petroleum ether/Et_2O) furnished **6** (67 mg, 0.118 mmol, 59% yield) as a colorless oil. Analytical data for **6**: IR (thin film, cm^{-1}) 2929, 2855, 2360, 2124, 1739, 1691, 1607, 1578, 1495, 1017; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 6.6 Hz, 2H), 7.51−7.49 (m 1H), 7.49−7.36 (m, 4H), 7.25−7.19 (m, 3H), 3.79 (d, J = 10.2 Hz, 1H), 3.60 (dd, J = 10.2, 18.0 Hz, 1H), 3.47 (d, J = 18.0 Hz, 1H), 2.70 (d, J = 16.8 Hz, 1H), 2.24 (d, J = 17.4 Hz, 1H), 1.40 (s, 9H), 1.39 (s, 9H), 0.92 (s, 9H), 0.39 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 172.3, 169.0, 140.0, 137.2, 132.8, 130.2, 130.0, 128.5, 128.0, 127.9, 127.5, 126.9, 81.7, 80.5, 80.3, 49.1, 44.4, 40.6, 28.1 (2 peaks), 27.8, 26.5, 26.3, 19.2, −2.1, −2.6; TLC (10:90 EtOAc/petroleum ether) R_f 0.52; LRMS (ESI) calculated for $C_{33}H_{48}O_6SiNa$ 591.31, found 591.33; HRMS (ESI) calculated for $C_{33}H_{48}O_6SiCs$ 701.2274, found 701.2262.

Di-*tert*-butyl 2-((*tert*-Butyldimethylsilyl)oxy)-2-(1-(furan-2-yl)-3-oxo-3-phenylpropyl)succinate (7). General procedure A was performed using (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (29 mg, 0.145 mmol, 1.0 equiv). ^1H NMR analysis of the crude mixture revealed a diastereomeric ratio of 4.9:1. Purification by flash chromatography (97:3 hexanes/Et_2O) furnished **35e** (53 mg, 0.0948 mmol, 65% yield) as a clear oil (the major diastereomer could be isolated as a pale yellow solid (mp 71−77 °C)). Analytical data for **35e**: IR (thin film, cm^{-1}) 2930, 2855, 1741, 1692, 1598, 1472, 1393, 1368, 1251, 1149, 1106, 1012; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = Hz, 2H), 7.53 (t, J = 7 Hz, 1H), 7.44−7.40 (m, 2H), 7.28 (s, 1H), 6.24 (d, J = 2 Hz, 1H), 6.14 (d, J = 3.5 Hz, 1H), 3.95 (dd, J = 2, 10.5 Hz, 1H), 3.66 (dd, J = 10.5, 17.5 Hz, 1H), 3.31 (dd, J = 2, 17 Hz, 1H), 2.92 (d, J = 16.5 Hz, 1H), 2.45 (d, J = 17 Hz, 1H), 1.43 (s, 9H), 1.39 (s, 9H), 0.87 (s, 9H), 0.33 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 171.9, 168.9, 153.1, 141.4, 137.0, 132.9, 128.5, 128.0, 110.2, 108.5, 81.7, 80.3, 79.8, 43.6, 43.3, 28.1, 27.7, 26.2, 19.0, −2.4, −2.9; TLC (10:90 EtOAc/petroleum ether) R_f 0.45; LRMS (ESI) calculated for $C_{31}H_{46}O_7SiNa$ 581.29, found 581.31; HRMS (ESI) calculated for $C_{31}H_{46}O_7SiCs$ 691.2067, found 691.2061.

Di-*tert*-butyl 2-((*tert*-Butyldimethylsilyl)oxy)-2-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)succinate (8). General procedure A was performed using 4-chlorochalcone (49 mg, 0.200 mmol, 1.0 equiv). ^1H NMR analysis of the crude mixture revealed a diastereomeric ratio of 3.8:1. Purification by flash chromatography (97:3 petroleum ether/Et_2O) furnished **8** (83 mg, 0.138 mmol, 69% yield) as a clear oil. Analytical data for **8**: IR (thin film, cm^{-1}) 2954, 2856, 2360, 1739, 1597, 1580, 1449, 1393, 1015; ^1H NMR (major diastereomer) (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.5 Hz, 2H), 7.55−

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7.20 (m, 7H), 3.77 (dd, J = 3.0, 9.9 Hz, 1H), 3.55 (dd, J = 10.2, 18 Hz, 1H), 3.44 (dd, J = 3.0, 17.7 Hz, 1H), 2.62 (d, J = 17.1 Hz, 1H), 2.20 (d, J = 16.8 Hz, 1H), 1.42 (s, 9H), 1.39 (s, 9H), 0.92 (s, 9H), 0.39 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.2, 172.1, 168.8, 138.5, 136.8, 133.1, 132.8, 132.1, 131.2, 128.6, 128.1, 127.9, 121.0, 82.0, 80.5, 80.3, 48.3, 44.4, 40.6, 32.4, 28.0, 27.7, 26.4, 24.9, 19.2, −2.2, −2.6; TLC (10:90 EtOAc/petroleum ether) R_f 0.45; HRMS (ESI) calculated for $C_{33}H_{47}ClO_6SiCs$ 735.1884, found 735.1892.

Di-*tert*-butyl 2-((*tert*-Butyldimethylsilyl)oxy)-2-(3-oxo-3-phenyl-1-(4-(trifluoromethyl)phenyl)propyl)succinate (9). General procedure A was performed using (*E*)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (40 mg, 0.145 mmol, 1.0 equiv). ^{1}H NMR analysis of the crude mixture revealed a diastereomeric ratio of 2.7:1. Purification by flash chromatography (97:3 hexanes/Et_2O) furnished **9** (49 mg, 0.0769 mmol, 53% yield) as a clear oil. Analytical data for **9**: IR (thin film, cm^{-1}) 2931, 2359, 1741, 1618, 1472, 1394, 1325, 1255, 1222, 1164, 1069, 1019; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.53−7.50 (m, 5H), 7.44−7.40 (m, 2H), 3.88 (dd, J = 2.4, 10.2 Hz), 3.58 (t, J = 10.2 Hz, 1H), 3.51 (dd, J = 3, 18 Hz, 1H), 2.63 (d, J = 17.4 Hz, 1H), 2.22 (d, J = 17.4 Hz, 1H), 1.42 (s, 9H), 1.40 (s, 9H), 0.93 (s, 9H), 0.39 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.5, 171.8, 168.6, 136.8, 133.1, 130.3, 128.6, 127.8, 124.9, 82.1, 80.6, 80.2, 48.6, 44.4, 40.6, 28.1, 27.7, 26.5, 19.2, −2.2, −2.6; TLC (10:90 EtOAc/petroleum ether) R_f 0.45; LRMS (ESI) calculated for $C_{34}H_{47}F_3O_6SiNa$ 659.30, found 659.32; HRMS (ESI) calculated for $C_{34}H_{47}F_3O_6SiCs$ 769.2148, found 769.2175.

(*E*)-Di-*tert*-butyl 2-((*tert*-Butyldimethylsilyl)oxy)-2-(3-oxo-1,5-diphenylpent-4-en-1-yl)succinate (10). General procedure A was performed using dibenzylideneacetone (62 mg, 0.265 mmol, 1.0 equiv). ^{1}H NMR analysis of the crude mixture revealed a diastereomeric ratio of 2.4:1. Purification by flash chromatography (60:40 petroleum ether/CH_2Cl_2 to 0:100 petroleum ether/CH_2Cl_2 linear gradient) furnished **10** (66 mg, 0.111 mmol, 42% yield) as a clear oil. Analytical data for **10**: IR (thin film, cm^{-1}) 2930, 2855, 1740, 1613, 1496, 1455, 1393, 1368, 1254, 1152, 1104; ^{1}H NMR (major diastereomer) (600 MHz, $CDCl_3$) δ 7.47−7.34 (m, 9H), 7.27−7.20 (m, 2H), 6.56 (d, J = 16.2 Hz, 1H), 3.67, (dd, J = 3.0, 10.8 Hz, 1H), 3.26 (dd, J = 10.8, 16.8 Hz, 1H), 3.14 (dd, J = 3.0, 16.8 Hz, 1H), 2.68 (d, J = 16.8 Hz, 1H), 2.25 (d, J = 16.8 Hz, 1H), 1.42 (s, 9H), 1.39 (s, 9H), 0.93 (s, 9H), 0.37 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 172.1, 168.9, 142.3, 139.8, 134.5, 130.3, 130.0, 128.9, 128.8, 128.2, 128.0, 127.0, 126.4, 81.7, 80.5, 80.2, 49.4, 44.2, 42.7, 28.1, 27.8, 27.4, 26.5, 25.7, 25.6, 19.2, −2.2, −2.6; TLC (10:90 EtOAc/petroleum ether) R_f 0.39; LRMS (ESI) calculated for $C_{35}H_{50}O_6SiCs$ 727.25, found 727.27; HRMS (ESI) calculated for $C_{35}H_{50}O_6SiCs$ 727.2431, found 727.2432.

(*E*)-Di-*tert*-butyl 2-(1,5-Bis(4-methoxyphenyl)-3-oxopent-4-en-1-yl)-2-((*tert*-butyldimethylsilyl)oxy)succinate (11). General procedure A was performed using dianisylideneacetone (59 mg, 0.200 mmol, 1.0 equiv). ^{1}H NMR analysis of the crude mixture revealed a diastereomeric ratio of 1.9:1. Purification by flash chromatography (95:5 to 85:15 petroleum ether/Et_2O gradient) furnished **11** (52 mg, 0.0794 mmol, 40% yield) as a clear oil. Analytical data for **11**: IR (thin film, cm^{-1}) 2930, 2854, 1740, 1658, 1602, 1513, 1463, 1422, 1393, 1107, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.37(m, 3H), 7.27−7.25 (m, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 16.4 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.61 (dd, J = 2.4, 10.4 Hz, 1H), 3.20 (dd, J = 10.8, 16.8 Hz, 1H), 3.06 (dd, J = 2.8, 16.8 Hz, 1H), 2.65 (d, J = 17.2 Hz, 1H), 2.22 (d, J = 16.8 Hz, 1H), 1.43 (s, 9H), 1.39 (s, 9H), 0.93 (s, 9H), 0.37 (s, 3H), 0.16 (s, 0.16); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.3, 172.3, 169.0, 161.5, 158.5, 142.1, 131.8, 130.9, 130.0, 127.2, 124.3, 114.3, 113.4, 81.6, 80.6, 80.2, 55.4, 55.2, 48.8, 44.3, 42.6, 28.1, 27.8, 26.5, 19.2, −2.1, −2.6; TLC (10:90 EtOAc/petroleum ether) R_f 0.18; LRMS (ESI) calculated for $C_{37}H_{54}O_8SiNa$ 677.35, found 677.37; HRMS (ESI) calculated for $C_{37}H_{54}O_8SiCs$ 787.2642, found 787.2623.

(*E*)-Di-*tert*-butyl 2-(1,5-Bis(3,5-dimethoxyphenyl)-3-oxopent-4-en-1-yl)-2-((*tert*-butyldimethylsilyl)oxy)succinate (12). General procedure A was performed using (1*E*,4*E*)-1,5-bis(3,5-dimethoxyphenyl)-1,4-pentadien-3-one (60 mg, 0.169 mmol, 1.0 equiv). ^{1}H NMR analysis of the crude mixture revealed a diastereomeric ratio of 1.6:1. Purification by flash chromatography (85:15 petroleum ether/Et_2O) furnished **12** (50 mg, 0.0699 mmol, 41% yield) as a clear oil. Analytical data for **12**: IR (thin film, cm^{-1}) 2929, 2850, 1740, 1651, 1595, 1463, 1428, 1368, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.33 (m, 1H), 6.61−6.47 (m, 6H) 6.28 (d, J = 18.4 Hz, 1H), 3.80 (s, 6H), 3.75 (s, 6H), 3.48 (d, J = 7.2 Hz, 1H), 3.26−3.14 (m, 2H), 2.71 (d, J = 17.2 Hz, 1H), 2.35 (d, J = 17.2 Hz, 1H), 1.42 (s, 9H), 1.40 (s, 9H), 0.95 (s, 9H), 0.36 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.1, 172.1, 169.0, 160.9, 160.3, 142.3 (2 peaks), 136.4, 126.9, 108.2, 106.0, 102.6, 98.8, 81.7, 80.3 (2 peaks), 55.4 (2 peaks), 49.7, 43.9, 42.6, 28.1, 27.7, 26.5, 19.2, −2.3, −2.6; TLC (10:90 EtOAc/petroleum ether) R_f 0.11; LRMS (ESI) calculated for $C_{39}H_{58}O_{10}SiNa$ 737.37, found 737.39; HRMS (ESI) calculated for $C_{39}H_{58}O_{10}SiCs$ 847.2853, found 847.2825.

(*E*)-Di-*tert*-butyl 2-((*tert*-Butyldimethylsilyl)oxy)-2-(1,5-di(furan-2-yl)-3-oxopent-4-en-1-yl)succinate (5-*syn*). General procedure A was performed using difurylideneacetone (29 mg, 0.136 mmol, 1.0 equiv). ^{1}H NMR analysis of the crude mixture revealed a diastereomeric ratio of 3.5:1. Purification by flash chromatography (97:3 hexanes/Et_2O) furnished **5** (41 mg, 0.0713 mmol, 52% yield) as a clear oil. Analytical data for **5**: IR (thin film, cm^{-1}) 2855, 1739, 1614, 1555, 1473, 1369, 1150, 1107, 1017; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.30 (d, J = 1.2 Hz, 1H), 7.23 (d, J = 15.9 Hz, 1H), 6.62 (d, J = 3.3 Hz, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.46 (dd, J = 1.8, 3.6 Hz, 1H), 6.25 (dd, J = 1.8, 3.0 Hz, 1H), 6.13 (d, J = 3.0 Hz, 1H), 3.81 (dd, J = 2.7, 11.1 Hz, 1H), 3.23−3.15 (m, 1H), 2.97 (dd, J = 2.4, 16.5 Hz, 1H), 2.89 (d, J = 16.8 Hz, 1H), 2.42 (d, J = 16.8 Hz, 1H), 1.44 (s, 9H), 1.42 (s, 9H), 0.87 (s, 9H), 0.30 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 171.8, 168.9, 152.9, 151.1, 144.8, 141.4, 128.6, 123.2, 115.6, 112.5, 110.2, 108.6, 81.7, 80.3, 79.7, 43.6, 43.4, 40.5, 28.1, 28.0, 27.9, 27.8, 27.7, 26.2, 19.0, −2.5, −2.9; TLC (10:90 EtOAc/petroleum ether) R_f 0.44; LRMS (ESI) calculated for $C_{31}H_{46}O_8SiNa$ 597.29, found 597.30; HRMS (ESI) calculated for $C_{31}H_{46}O_8SiCs$ 707.2016, found 707.2075.

(*E*)-Di-*tert*-butyl 2-((*tert*-Butyldimethylsilyl)oxy)-2-(1,5-di(furan-2-yl)-3-oxopent-4-en-1-yl)succinate (5-*anti*). To a solution of LiCl (37 mg, 0.88 mmol, 8.0 equiv, 0.67 M) in THF was added iPr_2NH (20 μL, 0.14 mmol, 1.3 equiv). The solution was cooled to 0 °C, and ^{n}BuLi (80 μL, 0.13 mmol, 1.654 M in hexanes, 1.2 equiv) was added. The solution was stirred at 0 °C for 10 min and then stirred at room temperature for 10 min. The solution was cooled to −78 °C, and a solution of **4** (63 mg, 0.110 mmol, 1.0 equiv) in THF (0.1 M) was added. The solution was allowed to slowly warm to room temperature over 3 h and then stirred at room temperature for 14−24 h. The reaction was diluted with Et_2O (15 mL) and quenched with saturated NH_4Cl (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (97:3 hexanes/diethyl ether) furnished **5-*anti*** (20 mg, 0.0348 mmol, 32% yield) as a yellow oil in a 5.5:1 dr. Analytical data for **5-*anti***: IR (thin film, cm^{-1}) 3420, 2920, 1733, 1635, 1507, 1265,1149, 1017; ^{1}H NMR (400 MHz, $CDCl_3$); 7.48 (d, J = 1.6 Hz, 1H), 7.27 (d, J = 16.0 Hz, 1H), 6.63 (d, J = 3.6 Hz, 1H), 6.59 (d, J = 15.6 Hz, 1H), 6.47 (dd, J = 1.6, 2.0 Hz, 1H), 6.23 (dd, J = 1.2, 2.0 Hz, 1H), 6.01 (d, J = 3.2 Hz, 1H), 3.92 (dd, J = 4.0, 10.0 Hz, 1H), 3.24−3.13 (m, 2H), 3.17 (d, J = 2.8 Hz, 1H), 2.88 (d, J = 16.0 Hz, 1H), 2.63 (d, J = 16.4 Hz, 1H), 1.44 (s, 9H), 1.41 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 170.9, 168.5, 153.2, 151.1, 144.8, 140.9, 128.6, 123.3, 115.6, 112.5, 110.2, 108.4, 81.8, 80.6, 79.6, 44.5, 43.3, 39.9, 28.1, 27.8, 26.1, 18.9, −2.6, −2.8; TLC (10:90 EtOAc/petroleum ether) R_f 0.31; HRMS (ESI) calculated for $C_{31}H_{46}O_8SiNa$ 597.2962, found 597.2866.

(1*S*,2*R*)-2-Phenylcyclohexyl *tert*-Butyldimethylsilyl Glyoxylate. The standard protocol[20] was followed using (1*S*,2*R*)-2-phenylcyclohexanol.[41] The silyl glyoxylate was obtained in 69% overall yield. Analytical data: IR (thin film, cm^{-1}): 3031, 2932, 2859,1736,

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1714, 1658, 1494, 1464, 1450, 1364, 1258, 1005, 842, 785, 755, 699; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30−7.26 (m, 2H), 7.22−7.15 (m, 3H), 5.14 (dt, J = 10.2, 4.2 Hz, 1H), 2.76 (dt, J = 12, 3.6 Hz, 1H), 2.19−2.13 (m, 1H), 1.97−1.92 (m, 1H), 1.90−1.84 (m, 1H), 1.82−1.77 (m, 1H), 1.62−1.45 (m, 3H), 1.42−1.32 (m, 1H), 0.78 (s, 9H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 231.9, 162.4, 142.4, 128.4, 127.5, 126.7, 77.6, 49.5, 34.1, 32.1, 26.2, 25.6, 24.7, 16.8, −7.2, −7.3; TLC (10% EtOAc/hexanes) R_f 0.5 (UV/CAM; also visible to naked eye); LRMS (ESI) calculated for $C_{20}H_{30}O_3SiNa$ 369.19, found 369.19; HRMS (ESI) calculated for $C_{20}H_{30}O_3SiCs$ 479.1019, found 479.1047.

4-*tert*-Butyl 1-((1*S*,2*R*)-2-Phenylcyclohexyl) 2-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-1,5-di(furan-2-yl)-3-oxopent-4-en-1-yl)succinate (13). General procedure A was performed using difurylideneacetone (29 mg, 0.134 mmol, 1.0 equiv) and (1*S*,2*R*)-2-phenylcyclohexyl *tert*-butyldimethylsilyl glyoxylate (98 mg, 0.281 mmol, 2.1 equiv). ^{1}H NMR analysis of the crude mixture revealed a diastereomeric ratio of 4.8:1 (**13**:Σ others). Purification by flash chromatography (95:5 petroleum ether/Et_2O) furnished **13** (73 mg, 0.108 mmol, 80% yield) as a clear oil. Analytical data for **13**: IR (thin film, cm^{-1}) 2931, 2856, 2359, 1740, 1614, 1555, 1474, 1391, 1365, 1254, 1151, 1105, 1015; ^{1}H NMR (major diastereomer) (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.28−7.14 (m, 5H), 7.07−6.95 (m, 2H), 6.64 (d, J = 3.0 Hz, 1H), 6.52 (d, J = 1.5 Hz, 1H), 6.29 (d, J = 15.5 Hz, 1H), 6.22 (s, 1H), 6.01 (d, J = 3.0 Hz, 1H), 5.31−5.23 (m, 1H), 3.43 (dd, J = 2.5, 11.5 Hz, 1H), 2.89 (dd, J = 12, 17.5 Hz, 1H), 2.73−2.68 (m, 1H), 2.67 (d, J = 16.5 Hz, 1H), 2.32 (d, J = 16.5 Hz, 1H), 2.28 (dd, J = 3.5, 12 Hz, 1H), 1.89 (dd, J = 13.5, 24 Hz, 2H), 1.77 (d, J = 13 Hz, 1H), 1.61−1.28 (m, 5H), 1.43 (s, 9H), 0.81 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 172.0, 168.7, 153.1, 151.3, 144.6, 142.9, 128.6, 127.6, 127.4, 126.7, 124.0, 115.0, 112.4, 110.0, 108.1, 80.5, 79.6, 49.9, 45.2, 42.1, 39.8, 35.1, 31.8, 28.1, 26.1, 25.8, 24.8, 18.9, −2.5, −2.7; TLC (10:90 EtOAc/petroleum ether) R_f 0.26; LRMS (ESI) calculated for $C_{39}H_{52}O_8SiNa$ 809.25, found 809.27; HRMS (ESI) calculated for $C_{39}H_{52}O_8SiCs$ 809.2485, found 809.2512.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ley, S. V.; Sheppard, T. D.; Myers, R. M.; Chorghade, M. S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1451−1472.

(2) Crimmins, M. T.; Long, A. *Org. Lett.* **2005**, *7*, 4157−4160.

(3) Fanjul, S.; Hulme, A. N. *J. Org. Chem.* **2008**, *73*, 9788−9791.

(4) Crimmins, M. T.; Stanton, M. G.; Allwein, S. P. *J. Am. Chem. Soc.* **2002**, *124*, 5958−5959.

(5) Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2005**, *70*, 9470−9479.

(6) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732−733.

(7) Wang, F.; Xiong, Y.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2007**, *349*, 2665−2668.

(8) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919−934.

(9) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Synthesis*; Wiley-VCH: Weinheim, 1997.

(10) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592−1604.

(11) Aitken, R. A.; Thomas, A. W. *Synlett* **1998**, 102−104.

(12) Shibata, I.; Yasuda, K.; Tanaka, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **1998**, *63*, 1334−1336.

(13) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582−2590.

(14) Jang, D.-P.; Chang, J.-W.; Uang, B.-J. *Org. Lett.* **2001**, *3*, 983−985.

(15) Blay, G.; Fernández, I.; Monje, B.; Pedro, J. R.; Ruiz, R. *Tetrahedron Lett.* **2002**, *43*, 8463−8466.

(16) Olivella, A.; Rodriguez-Escrich, C.; Urpi, F.; Vilarrasa, J. *J. Org. Chem.* **2008**, *73*, 1578−1581.

(17) Kanemasa, S.; Nomura, M.; Wada, E. *Chem. Lett.* **1991**, *20*, 1735−1738.

(18) Andrus, M. B.; Ye, Z. *Tetrahedron Lett.* **2008**, *49*, 534−537.

(19) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197−201.

(20) Nicewicz, D. A.; Brétéché, G.; Johnson, J. S. *Org. Synth.* **2008**, *85*, 278−286.

(21) Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170−6171.

(22) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84.

(23) Greszler, S. N.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 17393−17395.

(24) Steward, K. M.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 2864−2867.

(25) Yao, M.; Lu, C.-D. *Org. Lett.* **2011**, *13*, 2782−2785.

(26) Boyce, G. R.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8930−8933.

(27) For the utility of conjugate adducts of dialkylidene acetones, see: Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214−2215.

(28) Laroche, M.-F.; Belotti, D.; Cossy, J. *Org. Lett.* **2004**, *7*, 171−173.

(29) Lin, N.; Chen, M.-M.; Luo, R.-S.; Deng, Y.-Q.; Lu, G. *Tetrahedron: Asymmetry* **2010**, *21*, 2816−2824.

(30) Hevia, E.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 6448−6450.

(31) Kolonko, K. J.; Wherritt, D. J.; Reich, H. J. *J. Am. Chem. Soc.* **2011**, *133*, 16774−16777.

(32) Giampietro, N. C.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12556−12557.

(33) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 5301−5303.

(34) Schmitt, D. C.; Lam, L.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 5136−5139.

(35) CCDC 854999 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.cif.

(36) Stereochemistry of the remaining enones was assigned by analogy. In each case the major diastereomer was less polar than the minor diastereomer. In the ^{1}H NMR spectra, the stereogenic methine H was further upfield in the major diastereomer in all cases.

(37) For further evidence of (*Z*)-glycolate enolate generation from silyl glyoxylates, see: Schmitt, D. C.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 944−947.

(38) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157−172.

(39) Mayr, H.; Breugst, M.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6470−6505.

(40) We have previously proposed stabilization of the (*E*)-form of enolates such as **2** by chelation from the g-ester functionality: Greszler, S. N.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3689−3691.

(41) Gonzalez, J.; Aurigemma, C.; Truesdale, L.; Denmark, S. E.; Tymonko, S. A.; Cottell, J. J.; Gomez, L. *Org. Synth.* **2002**, *79*, 93−98.