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Note

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Doubly Vinylogous Aldol Reaction of Furoate Esters with Aldehydes and Ketones

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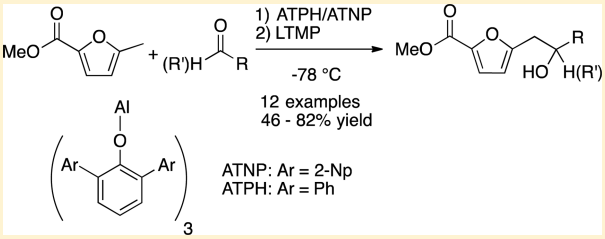
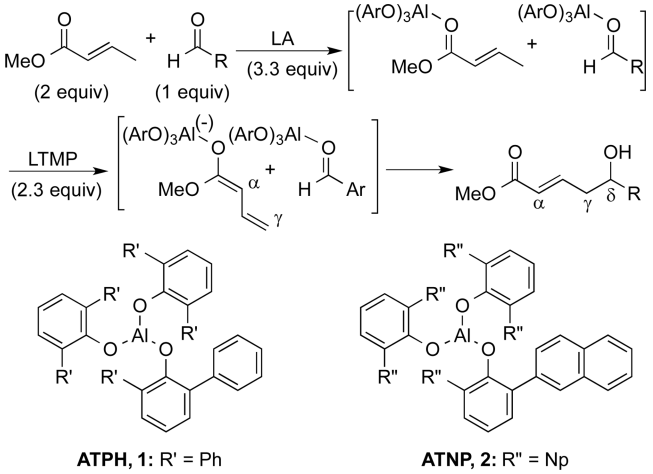
Supporting Information

ABSTRACT: The use of bulky Lewis acids, aluminum tris(2,6-diphenylphenoxide) (ATPH) and aluminum tris(2,6-di-2-naphthylphenoxide) (ATNP), in the doubly vinylogous aldol reaction between methyl-5-methyl-2-furoate and aldehydes or ketones is described. These reactions proceed smoothly and in high yields with both enolizable and non-enolizable substrates. This C−C bond-forming reaction enables a new bond construction for the synthesis of functionalized furans.



The vinylogous aldol reaction is an extension of the aldol reaction,[1,2] wherein one or more alkenes intercede in the enolate precursor between the site of enolization and the carbonyl.[3,4] The parent transformation produces a functionally dense δ-hydroxy-α,β-unsaturated carbonyl compound and provides a useful synthetic disconnection for complex molecule synthesis. This transformation has been the subject of much research, and enantioselective methods using silicone dienolates with either Lewis acid,[5] metal,[6] or nucleophilic catalysis[7] have been reported, as have more direct metalo-enolate-derived methods[8] as well as enantioselective methods.[9] An important advance in this field was the application of Yamamoto's bulky Lewis acid, aluminum tris(2,6-diphenylphenoxide) (ATPH, **1**, Scheme 1), to this reaction.[10−14] ATPH blocks reactivity at the α-carbon of the enolate and directs reactivity to the distal carbon for substrates as large as hexaenolates.[11] Furthermore, ATPH has been used in intramolecular vinylogous aldol reactions to form medium and large membered rings, as well as for the synthesis of the macrocyclic core of the antimitotic natural product, peloruside A.[15,16] With these new bond constructions, chemists have greater options to tackle synthetic problems from different approaches, and in this note, we extend the use of ATPH and its homologue, aluminum tris(2,6-di-2-naphthylphenoxide) (ATNP),[17] to doubly vinylogous aldol reactions of methyl-5-methyl-2-furoate (**3**) and various aldehydes and ketones.[18] Compound **3** can serve as an enolate precursor via deprotonation of the exocyclic methyl group and enolization through the diene of the furoate. The related enolization of a toluene derivative has been described by Yamamoto.[10] This approach similarly adds to the arsenal of synthetic chemists and allows for bond constructions that were previously unknown. Noteworthy is that the furan group provides an excellent handle for synthetic manipulations via electrophilic functionalization,[19] oxidative transformations,[20] and cycloaddition chemistry.[21] Further, the use of ketones in aldol reactions can be problematic,[3] and in this note, we demonstrate the applicability of this method to ketone electrophiles.

Scheme 1. Vinylogous Aldol Reaction with ATPH/ATNP



ATPH, 1: R' = Ph

ATNP, 2: R" = Np

Yamamoto's protocol for vinylogous aldol reactions using ATPH requires that both reactants be precomplexed with the Lewis acid prior to the addition of base (Scheme 1).[10−14] With ATPH and ester enolate precursors, the reaction is limited to non-enolizable aldehydes;[10,11] however, recent work in this lab utilizing the aforementioned Lewis acid, ATNP (**2**, Scheme 1), has extended the scope to include enolizable aldehydes with ester-derived enolates.[17] We ascribe the difference in the reactivity of ATPH and ATNP to the greater reach of ATNP resulting in more effective blocking of the α-protons of the enolizable aldehyde. Further, we observed an atypical ability of ATPH and ATNP to promote these reactions; ordinary alkyl aluminum Lewis acids and a host of other bulky aluminum Lewis acids developed by Yamamoto have been studied and

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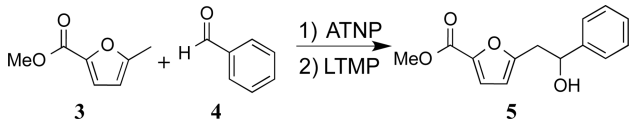
found to provide diminished yields.[17] We, therefore, began our investigations using furoate **3**[22] and benzaldehyde and applied the optimized conditions discovered in our previous work on the parent vinylogous aldol reaction using ATNP as the promoter (Table 1).[17] These conditions consisted of treating a

Table 1. Optimization of Reaction Conditions[a]



3 **4** **5**

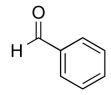
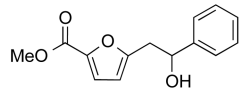
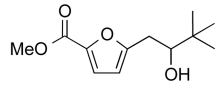
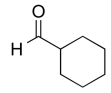
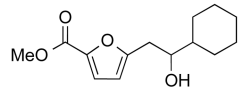
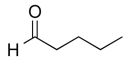
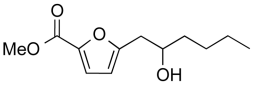
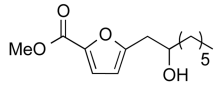
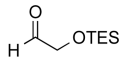
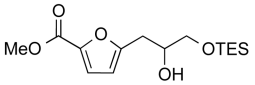
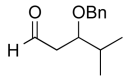
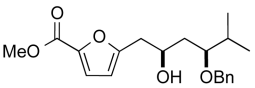
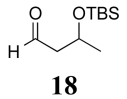
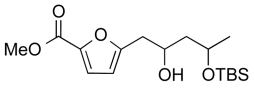
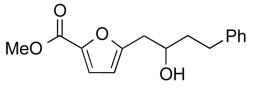
entry	ester (equiv)	ATNP (equiv)	LTMP (equiv)	temp (°C)	yield (%)
1	2.0	3.3	2.3	−78	56
2	2.0	3.3	3.0	−78	55
3	2.0	3.3	3.5	−78	78
4	2.0	3.3	5.0	−78	80
5	1.0	0	1.2	−78	trace

[a]Reaction conditions: 1 equiv of aldehyde, 3.3 equiv of ATNP, −78 °C, 10:1 toluene−THF.

mixture of 2 equiv of ester, 1 equiv of aldehyde, and 3.3 equiv of ATNP with 2.3 equiv of LTMP (lithium 2,2,6,6-tetramethylpiperide) at −78 °C in 10:1 toluene−THF, which provided the desired product (**5**) in a yield of 56% (Table 1, entry 1). We speculated that the modest yield was due to incomplete enolization of the furoate as it is anticipated to be less acidic than typical esters due to loss of aromaticity upon enolization. We, therefore, studied the use of greater quantities of base and observed product formation in 55, 78, and 80% yields when using 3.0, 3.5, and 5.0 equiv of LTMP, respectively (Table 1, entries 2−4). Attempts to run the reaction in the absence of ATNP provided trace amounts of product with recovery of the aldehyde and multiple unidentified furoate-derived resonances by NMR (Table 1, entry 5). Given that the differences in yields obtained using 3.5 and 5.0 equiv of base are within experimental error, we settled on the use of 3.5 equiv for further studies.

We applied our optimized conditions to a variety of substrates, as shown in Table 2. We found that both branched and unbranched aliphatic aldehydes are good reaction partners and provide the products in yields ranging from 71 to 81% (Table 2, entries 2−5). Aldehydes with oxygenation at the α- or β-positions were also studied and provided moderate to high yields; triethylsiloxyacetaldehyde (**14**), an α-oxygenated aldehyde, provided the desired product in a modest yield of 52% (Table 2, entry 6), while β-benzyloxyaldehyde **16** provided the product in a high yield of 85% but with a moderate diastereoselectivity of 3.4:1, favoring the syn isomer (Table 2, entry 7). Aldehyde **18**, which bears a β-*tert*-butyldimethylsilyloxy group, provided a relatively low yield of 46% and a diastereoselectivity of 1.5:1 (Table 2, entry 8). A curious outlier was hydrocinnamaldehyde, which provided the product in a low yield of 27% with unreacted aldehyde in the recovered reaction mixture (Table 2, entry 9). This result could either be due to this being a poor substrate or to the substrate inhibiting the reactivity of the enolate by an unknown mechanism. In order to distinguish between these possibilities, we performed a competition experiment using 4 equiv of furoate and 1 equiv each of valeraldehyde and hydrocinnamaldehyde. We observed that the two desired products were formed in a 10:1 ratio with the valeraldehyde-derived product, **11**, predominating, indicating that hydrocinnamaldehyde is a poor substrate but does not inhibit the reaction.

Table 2. ATNP Aldehyde Scope[a]

entry	aldehyde	product	% yield (dr)
1	 **4**	 **5**	78
2	 **6**	 **7**	81
3	 **8**	 **9**	78
4	 **10**	 **11**	72
5	 **12**	 **13**	71
6	 **14**	 **15**	52
7	 **16**	 **17**	85 (3.4:1)
8	 **18**	 **19**	46 (1.5:1)
9	 **20**	 **21**	27

[a]Reaction conditions: 2 equiv of ester, 1 equiv of aldehyde, 3.3 equiv of ATNP, 3.5 equiv of LTMP, −78 °C, 10:1 toluene−THF.

We also studied the use of ketones as partners in this reaction (Table 3). 2-Butanone was chosen as a model substrate, and the outcome of the reaction with furoate **3** was studied using ATNP or ATPH under our standard reaction conditions. We found that when using ATNP the desired product (**23**) was obtained in 68% yield, whereas with ATPH, it was obtained in only 27% yield (Table 3, entry 1). We used ATNP for further studies and examined three other methyl ketones in this reaction, all of which provided the products in useful yields (Table 3, entries 2−4). β-Benzyloxyketone **26** afforded the product in 51% yield, indicating that β-oxygenation is tolerated. Interestingly, hydrocinnamyl ketone **28** was a good reaction

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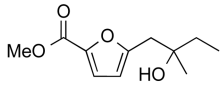
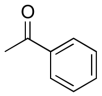
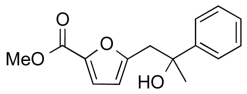
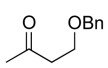
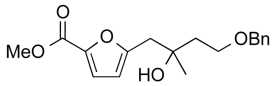
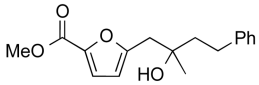
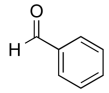
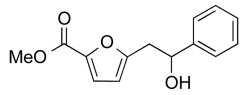
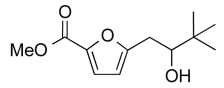
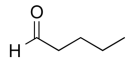
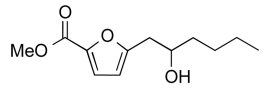
Table 3. ATNP Ketones[a]

entry	ketone	product	yield (%)
1	 **22**	 **23**	68[a] 27[b]
2	 **24**	 **25**	50[a]
3	 **26**	 **27**	51[a]
4	 **28**	 **29**	58[a]

[a]Conditions: 2 equiv of ester, 1 equiv of aldehyde, 3.3 equiv of ATNP with 3.5 equiv of LTMP, −78 °C, 10:1 toluene−THF. [b]The reaction was run as above except with ATPH instead of ATNP.

Table 4. ATPH Reactions[a]

entry	substrate	product	yield (%)
1	 **4**	 **5**	78
2	 **6**	 **7**	82
3	 **10**	 **11**	25

[a]Reaction conditions: 2 equiv of ester, 1 equiv of aldehyde, 3.3 equiv of ATPH, 3.5 equiv of LTMP, −78 °C, 10:1 toluene−THF.

partner and provided the desired product in 58% yield (Table 3, entry 4). This stands in contrast to the reaction with hydrocinnamaldehyde, wherein the product was observed in only 27% yield, with the majority of the substrate not undergoing reaction. We expected ketone **28** to be a poor reaction partner given its structural similarity to hydrocinnamaldehyde and that ketones, in general, are less reactive electrophiles in aldol reactions. We therefore performed a competition experiment between hydrocinnamaldehyde and ketone **28**; consistent with expectations based on the reactivity of the individual substrates, we found that the products derived from ketone **28** and hydrocinnamaldehyde were obtained in a 3.7:1 ratio. This provides further evidence for the intrinsic lack of reactivity of hydrocinnamaldehyde in this reaction.

The cause of the poor reactivity of hydrocinnamaldehyde is unclear but may be related to the increased polarization of the carbonyl when bound to the Lewis acid and a resulting cation−π interaction with the phenyl group that would block the approach of the enolate. The greater steric hindrance afforded by the methyl group of ketone **28** would interfere with such a cation−π interaction, thereby freeing the carbonyl for attack by the enolate.

While ATPH was not as effective as ATNP in promoting the reaction with 2-butanone, we wished to test the use of this Lewis acid with aldehydes (Table 4). We found that ATPH is an effective promoter of the reaction with non-enolizable aldehydes providing the products in high yields (Table 4, entries 1 and 2). However, when we used valeraldehyde, the product was observed in only 25% yield (Table 4, entry 3). This result is consistent with the results of Yamamoto[10,11] and with our previous results,[17] wherein enolizable aldehydes were found to be poor substrates in reactions with ester-derived enolates using ATPH. As such, it would appear that reactions of enolizable aldehydes with ester-derived enolates require the increased steric bulk of ATNP.

In conclusion, we describe a new carbon−carbon bond-forming reaction between methyl-5-methyl furoate (**3**) and aldehydes or ketones. The transformation demonstrates the utility of the bulky Lewis acids ATPH and ATNP as promoters for doubly vinylogous aldol reactions through a furan ring. The yields for this process range from high to moderate, and a wide scope of aldehyde and ketone substrates are good partners, including sterically hindered, α- and β-branched, and α- and β-oxygenated substrates. This reaction provides a bond disconnection that we believe will be of practical use to the organic chemistry community.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven- or flame-dried glassware under a dry nitrogen atmosphere. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen prior to use. 2,2,6,6-Tetramethylpiperdine was distilled from sodium metal under nitrogen prior to use. Toluene and dichloromethane were distilled from calcium hydride under nitrogen prior to use. Acetone was dried by storage over 4 Å sieves for 2 days. Solvents were transferred via cannula. Commercially available aldehydes **4**, **6**, **8**, **10**, and **12** were distilled prior to use. Aldehydes **14**[23] and **18**[24] were prepared according to literature procedures. Aldehyde **16** was synthesized as described below. Commercially available ketones **20**, **22**, **24**, and **26** were distilled prior to use. Me_3Al (2.0 M solution in hexanes) was used as received. *n*-BuLi (1.6 M in hexanes) was titrated prior to use with menthol as the acid and 2,2′-bipyridine as the indicator. 2,6-Di-2-naphthylphenol was prepared according to a literature procedure.[17] This material was recovered from reactions and purified by recrystallization from hexanes/chloroform and dried by azeotropic distillation using distilled toluene. Residual toluene was removed under reduced pressure and the resulting solid dried by stirring under vacuum overnight. Methyl 5-methyl-2-furoate was prepared from commercially available 5-methylfurfural.[25] Column chromatography was carried out using 60 Å silica gel (37−75 μm) with ACS reagent grade solvents. ^{1}H NMR spectroscopy was performed at 500 MHz in $CDCl_3$ using residual $CHCl_3$ as an internal standard (7.27 ppm). ^{13}C NMR spectroscopy was performed at 75 MHz or at 100 MHz in $CDCl_3$ using residual $CHCl_3$ as an internal standard (77.26 ppm for the central peak). FT-IR spectra were collected as thin films on NaCl plates. Exact mass was determined using electrospray ionization (ESI-TOF). Ozone was generated using a Welsbach ozonator.

General Vinylogous Aldol Procedure with ATNP. *Preparation of ATNP.* Me_3Al (0.777 mL, 1.554 mmol, 2 M solution in hexanes) was

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added via syringe to a stirred solution of 2,6-dinaphthylphenol (1.615 g, 4.66 mmol) in freshly distilled toluene (40 mL) at room temperature. Vigorous bubbling was observed, and the solution turned yellow. After 20 min, the solution was cooled to −78 °C in a dry ice/acetone bath and used as described below.

Preparation of LTMP. To a stirred solution of 2,2,6,6-tetramethylpiperdine (0.278 mL, 1.649 mmol) in freshly distilled THF (4 mL) cooled to −78 °C in a dry ice/acetone bath was added *n*-BuLi (1.03 mL, 1.649 mmol, 1.6 M solution in hexanes) via syringe. The cold bath was removed, and the reaction was allowed to warm to 0 °C over a 20 min period. The solution was then recooled in a dry ice/acetone bath to −78 °C and allowed to stir 20 min longer and was then used as described below.

Vinylogous Aldol Procedure. Methyl-5-methyl-2-furoate (0.118 mL, 0.942 mmol) and the aldehyde (0.471 mmol) were added via syringe to the stirred solution of ATNP (prepared above) at −78 °C in a dry ice/acetone bath. After 20 min, the cold solution of LTMP (prepared above) was added dropwise via cannula to the ATNP complex over an approximately 2 min period. The solution turned opaque immediately. The reaction was allowed to stir for 3 h at −78 °C and was then quenched by the addition of hydrochloric acid (1 M), diluted with hexanes (10 mL), and stirred while being allowed to warm to room temperature. The biphasic mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide the desired compound plus recovered 2,6-dinaphthylphenol as a solid. The resulting solid was suspended in hexanes and warmed to reflux. Chloroform was added until the solution cleared, and the resulting yellow solution was cooled to room temperature and then chilled in an ice bath for 30 min to induce crystallization of the 2,6-dinaphthylphenol. The crystals were isolated by filtration, and the mother liquor was concentrated and purified by flash chromatography (10:1 hexanes/EtOAc to elute traces of residual 2,6-dinaphthylphenol and then 3:1 hexanes/EtOAc to elute the substrate) to provide the desired product.

General Vinylogous Aldol Procedure with ATPH. *Preparation of ATPH.* Me_3Al (0.777 mL, 1.554 mmol, 2 M solution in hexanes) was added via syringe to a stirred solution of 2,6-diphenylphenol (1.149 g, 4.66 mmol) in freshly distilled toluene (40 mL) at room temperature. Vigorous bubbling was observed, and the solution turned yellow. After 20 min, the solution was cooled to −78 °C in a dry ice/acetone bath and used as described below.

Vinylogous Aldol Procedure. Methyl-5-methyl-2-furoate (0.118 mL, 0.942 mmol) and the aldehyde (0.471 mmol) were added via syringe to the stirred solution of ATPH (prepared above) at −78 °C in a dry ice/acetone bath. After 20 min, the cold solution of LTMP (prepared above) was added dropwise via cannula to the ATNP complex over an approximately 2 min period. The solution turned opaque immediately. The reaction was allowed to stir for 3 h at −78 °C and was then quenched by the addition of hydrochloric acid (1 M), diluted with hexanes (10 mL), and stirred while being allowed to warm to room temperature. The biphasic mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide the desired compound plus recovered 2,6-dinaphthylphenol as a solid. The resulting solid was suspended in hexanes and warmed to reflux. Chloroform was added until the solution cleared, and the resulting yellow solution was cooled to room temperature and then chilled in an ice bath for 30 min to induce crystallization of the 2,6-diphenylphenol. The crystals were isolated by filtration, and the mother liquor was concentrated and purified by flash chromatography (10:1 hexanes/EtOAc to elute traces of residual 2,6-diphenylphenol and then 3:1 hexanes/EtOAc to elute the substrate) to provide the desired product.

*Methyl 5-(2-Hydroxy-2-phenylethyl)-2-furoate (**5**, Table 2).* Following the general vinylogous aldol procedure with ATNP, compound **5** was obtained as a yellow oil (0.090 g, 78% yield): R_f = 0.26 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.37−7.25 (m, 5H), 7.11 (d, J = 3.4 Hz, 1H), 6.21 (d, J = 3.4 Hz, 1H), 5.11 (X of ABX, J = 8.4, 4.9 Hz, 1H), 3.90 (s, 3H), 3.16 (A of ABX, J = 15.1, 8.5, 1H), 3.11 (B of ABX, J = 15.1, 4.9, 1H), 2.13 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 157.6, 143.6, 143.3, 128.8, 128.1, 125.9, 119.5, 110.1, 72.6, 52.2, 38.6; IR (thin film) 3442, 3030, 2951, 1720, 1519, 1437, 1383 cm^{-1}; HRMS (ESI) m/z calcd for $C_{28}H_{28}O_8Na$ [2M + Na]$^+$ 515.1677; found 515.1684.

*Methyl 5-(2-Hydroxy-3,3-dimethylbutyl)-2-furoate (**7**, Table 2).* Following the general vinylogous aldol procedure with ATNP, compound **7** was obtained as a colorless oil (0.086 g, 81% yield): R_f = 0.34 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.06 (d, J = 3.4 Hz, 1H), 6.22 (d, J = 3.4 Hz, 1H), 3.81 (s, 3H), 3.59 (X of ABX, J = 10.7, 1.8 Hz, 1H), 2.89 (A of ABX, J = 15.2, 1.8 Hz, 1H), 2.63 (B of ABX, J = 15.2, 10.7 Hz, 1H), 2.03 (s, 1H) 0.91 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 159.4, 143.4, 119.5, 109.5, 77.6, 51.9, 35.1, 31.5, 25.8; IR 3473, 2956, 2907, 2870, 1722, 1595, 1531, 1518, 1437, 1363 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_4Na$ [M + Na]$^+$ 249.1278; found 249.1284.

*Methyl 5-(2-Cyclohexyl-2-hydroxyethyl)-2-furoate (**9**, Table 2).* Following the general vinylogous aldol procedure with ATNP, compound **9** was obtained as a colorless oil (0.092 g, 78% yield): R_f = 0.37 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.13 (d, J = 3.4 Hz, 1H), 6.27 (d, J = 3.4 Hz, 1H), 3.88 (s, 3H), 3.80−3.74 (br m, 1H), 2.93 (A of ABX, J = 15.2, 3.3 Hz, 1H), 2.79 (B of ABX, J = 15.2, 9.3 Hz, 1H), 1.90−1.65 (m, 6H), 1.43−1.00 (m, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 158.9, 143.5, 119.5, 109.7, 74.3, 52.0, 43.6, 33.8, 29.3, 27.9, 26.6, 26.4, 26.3; IR 3448, 2926, 2852, 1720. 1519, 1310 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{20}O_4Na$ [M + Na]$^+$ 275.1254; found 275.1260.

*Methyl 5-(2-Hydroxyhexyl)-2-furoate (**11**, Table 2).* Following the general vinylogous aldol procedure with ATNP, compound **11** was obtained as pale yellow amorphous solid (0.077 g, 72% yield): R_f = 0.24 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.10 (d, J= 3.4 Hz, 1H), 6.24 (d, J = 3.4 Hz, 1H) 4.00−3.92 (m, 1H), 3.85 (s, 3H), 2.88 (A of ABX, J = 15.1, 4.1, 1H), 2.78 (B of ABX, J = 15.1, 8.1, 1H), 2.2−2.05 (br m, 1H), 1.5−1.22 (m, 6H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 158.3, 143.5, 119.4, 109.7, 70.2, 51.9, 36.8, 36.7, 27.8, 22.7, 14.1; IR 3435, 2955, 2931, 2860, 1721, 1519, 1437, 1382, 1310 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_4Na$ [M + Na]$^+$ 249.1098; found 249.1106.

*Methyl 5-(2-Hydroxyoctyl)-2-furoate (**13**, Table 2).* Following the general vinylogous aldol procedure with ATNP, compound **13** was obtained as a pale yellow amorphous solid (0.085 g, 71% yield): R_f = 0.31 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.11 (d, J = 3.4 Hz, 1H), 6.25 (d, J = 3.4 Hz, 1H), 3.97−3.90 (br m, 1H), 3.87 (s, 3H), 2.89 (A of ABX, J = 15.1, 4.1 Hz, 1H), 2.79 (B of ABX, J = 15.1, 8.1 Hz, 1H), 1.91 (br s, 1H), 1.50−1.19 (m, 10H), 0.88 (t, J = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 158.3, 143.6, 119.5, 109.8, 70.3, 52.0, 37.2, 36.7, 32.0, 29.4, 25.7, 22.8, 14.3; IR 3434, 2929, 2857, 1723, 1595, 1519, 1437, 1382, 1310 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{22}O_4Na$ [M + Na]$^+$ 277.1411; found 277.1411.

*Methyl 5-(2-Hydroxy-3-triethylsilyloxy-propyl)-2-furoate (**15**, Table 2).* Following the general vinylogous aldol procedure with ATNP, compound **15** was obtained as a colorless oil (0.077 g, 52% yield): R_f = 0.29 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.13 (d, J = 3.4 Hz, 1H), 6.29 (d, J = 3.4 Hz, 1H), 4.07−4.0 (br m, 1H), 3.89 (s, 3H), 3.68 (A of ABX, 10.0, 3.7 Hz, 1H), 3.51 (B of ABX, J = 10.0, 6.4 Hz, 1H), 2.88 (d, J = 6.5 Hz, 2H), 2.57 (d, J = 4.6 Hz, 1H), 0.97 (t, J = 8.0 Hz, 9H), 0.62 (q, J = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 157.7, 143.4, 119.4, 109.5, 70.2, 66.0, 51.9, 32.4, 6.8, 4.4; IR 3457, 2954, 2912, 2876, 1724, 1595, 1520 cm^{-1}; HRMS (ESI) m/z calcd for $C_{30}H_{52}O_{10}Si_2Na$ [2M + Na]$^+$ 651.2992; found 651.3000.

*Methyl 5-[4-(Benzyloxy)-2-hydroxy-5-methylhexyl]-2-furoate (**17**, Table 2).* Following the general vinylogous aldol procedure with ATNP, compound **17** was obtained as a colorless oil (0.139 g, 85% yield). This material was found to be a 3.4:1 mixture of diastereomers: R_f = 0.21 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38−7.28 (m, 5H, major and minor) 7.12 (d, J = 3.4 Hz, 1H, major and minor), 6.25 (d, J = 3.4 Hz, 1H, major), 6.23 (d, J = 3.4 Hz, 1H,

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minor), 4.68 (A of AB, J = 11.1 Hz, 1H, major), 4.59 (A of AB, J = 11.3 Hz, 1H, minor), 4.53 (B of AB, J = 11.3 Hz, 1H, minor), 4.42 (B of AB, J = 11.1 Hz, 1H, major), 4.26−4.20 (br m, 1H, minor), 4.19−4.12 (m, 1H, major), 3.94 (s, 3H, minor), 3.88 (s, 3H, major), 3.60 (ddd, J = 8.3, 5.9, 4.1 Hz, 1H, major), 3.50 (m, 1H, minor), 2.97−2.91 (ddd, J = 7.6, 6.2, 3.2 Hz, 1H, minor), 2.90−2.81 (ABX, obscured, 2H, minor), 2.87 (A of ABX, J = 15, 7.13 Hz, 1H, major), 2.81 (B of ABX, J = 15, 5.35 Hz, 1H, major) 2.21−2.12 (m, 1H, major), 2.10−2.01 (m, 1H, minor), 1.74−1.59 (m, 2H, major and minor), 0.96 (d, J = 6.8 Hz, 3H, minor), 0.93 (d, J = 7.0 Hz, 3H, major), 0.91−0.87 (m, 3H, major and minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 158.3, 143.4, 138.0, 128.8, 128.7, 128.3, 128.1, 128.1, 119.6, 119.6, 109.8, 109.7, 85.0, 82.0, 72.1, 71.2, 70.7, 67.7, 52.0, 36.9, 36.8, 35.4, 35.0, 30.3, 29.2, 19.3, 18.8, 17.7, 16.0; IR 3468, 2958, 1727, 1519, 1454, 1436 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{26}O_5Na$ $[M + Na]^+$ 369.1673; found 369.1672.

*Methyl 5-(2,4-Dihydroxy-5-methylhexyl)-2-furoate (**17a**).* Compound **17** (0.185 g, 0.534 mmol) was taken up in 5 mL of methanol, and 5% palladium on carbon (0.057 g) was added. The reaction was placed under an atmosphere of H_2 using a balloon and stirred for 16 h, filtered, and concentrated to give compound **17a** (0.133 g, 97% yield): R_f = 0.31 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, J = 3.4 Hz, 1H, major and minor), 6.28 (d, J = 3.4 Hz, 1H, major) 6.27 (d, J = 3.4 Hz, 1H, minor), 4.36−4.28 (m, 1H, minor) 4.26−4.19 (m, 1H, major), 3.88 (s, 3H, major and minor), 3.73−3.69 (m, 1H, minor), 3.67 (ddd, J = 10.4, 5.1, 2.0, 1H) 2.90−2.86 (m, 2H), 1.74−1.49 (m, 3h, major and minor), 0.95 (d J = 6.8, 3H, minor) 0.91 (d, J = 6.9, 6H, major) 0.89 (d J = 6.8, 3H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 158.1, 157.9, 143.7, 119.5, 110.0, 109.8, 78.0, 74.1, 71.5, 68.1, 39.19, 39.15, 37.2, 36.7, 34.5, 34.0, 18.8, 18.5, 18.1, 17.5; IR 3402, 2957, 1721, 1519, 1437, 1310 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{21}O_5$ $[M + H]^+$ 257.1387; found 257.1389.

*Methyl 5-[(6-Isopropyl-2,2-dimethyl-1,3-dioxan-4-yl)methyl]-2-furoate (**17b**).* Compound **17a** (0.100 g, 0.390 mmol) was taken up in a 1:1 mixture of dry acetone and 2,2-dimethoxypropane (0.323 g, 0.790 mL; 0.5M) over 4 Å molecular sieves. *p*-Toluenesulfonic acid monohydrate (0.038 g, 0.020 mmol, 0.05 equiv) was then added, and the reaction was stirred for 2 h. The reaction was diluted with 1:1 hexanes/EtOAc and washed with saturated sodium bicarbonate. The aqueous layer was back-extracted with 1:1 hexanes/EtOAc, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The crude material was purified using flash chromatography with a solvent gradient from 50:1 to 2:1 hexanes/EtOAc to provide **17b** (0.077 g, 0.26 mmol 67% yield). The major stereoisomer was assigned as *syn* using the ^{13}C NMR analysis method of Rychnovsky[26] with diagnostic resonances at 19.77 and 30.06 ppm. The minor diastereomer displayed diagnostic resonances at 24.68 and 24.22 ppm consistent with *anti*-product: R_f = 0.29 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.08 (d, J = 3.4 Hz, 1H, major and minor), 6.21(d, J = 3.4 Hz, 1H, major and minor), 4.17−4.06 (m, 1H, major and minor), 3.84 (s, 3H, major and minor), 3.45 (ddd, J = 11.6, 6.7, 2.3 Hz, 1H, major), 3.42−3.38 (m, obscured, 1H, minor), 2.91 (A of ABX, J = 15.2, 6.7 Hz, 1H, major), 2.75 (B of ABX, J = 15.2, 6.2 Hz, 1H, major), 2.94−2.75 (A and B of ABX, obscured, minor) 1.63−1.52 (m, 1H, major and minor), 1.43 (dt, J = 12.7, 2.5, Hz, 1H, major), 1.38 (s, 3H, major), 1.35 (s, 3H, major), 1.30 (d, J = 3.5 Hz, 6H, minor) 1.14 (dt, J = 12.7, 11.6 Hz, 1H, major), 0.88 (d, J = 6.6, 3H, major) 0.87 (d, J = 6.7, 3H, major), 0.81 (d, J = 6.8, 3H, major and minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 158.0, 157.6, 143.3, 119.4, 109.7, 109.3, 100.7, 98.8, 73.9, 71.8, 67.7, 65.2, 51.9, 36.1, 35.8, 34.9, 33.4, 33.1, 30.3, 24.9, 24.4, 20.0, 18.8, 18.5, 17.8, 17.7; IR 3422, 2989, 2956, 2873, 1732, 1531, 1519, 1436, 1379, 1307 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{24}O_5Na$ $[M + Na]^+$ 319.1522; found 319.1521.

*Methyl 5-[3-[tert-Bbutyl(dimethyl)silyl]oxy-2-hydroxy-4-methylpentyl]-2-furoate (**19**, Table 2).* Following the general vinylogous aldol procedure with ATNP, compound **19** was obtained as colorless oil (0.074 g, 46% yield): R_f = 0.14 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.14−7.11 (d overlapping, 1H, major and minor), 6.29−6.26 (d overlapping, 1H, major and minor), 4.40−4.33 (m, 1H, minor), 4.27−4.20 (m, 1H, minor), 4.18−4.05 (m, 2H, major), 3.88 (s, 3H, major and minor), 3.77 (m, 1H, major and minor), 2.89 (A of ABX, J = 15.1, 6.9 Hz, 1H, major and minor), 2.80 (B of ABX, J = 15.1, 6.2 Hz, 1H, major and minor), 1.75−1.68 (m, 1H, minor), 1.63−1.53 (m, 1H, major and minor), 1.23 (d, J = 6.3, 3H, minor), 1.18 (d, J = 6.1 Hz, 3H, major), 0.91−0.86 (m, 9H, major and minor), 0.11 (d, J = 7.1 Hz, 6H, major), 0.09 (d, J = 5.0 Hz, 6H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 158.3, 158.2, 143.43, 143.39, 119.53, 119.51, 109.8, 109.6, 70.2, 70.1, 67.8, 67.1, 51.9, 45.1, 43.6, 37.0, 36.7, 25.98, 25.96, 24.7, 22.8, 18.09, 18.05, −3.7, −4.4, −4.6, −4.9; IR 3495, 2955, 2930, 2856, 1724, 1519 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{30}O_5SiNa$ $[M + Na]^+$ 365.1755; found 365.1757.

*Methyl 5-(2-Hydroxy-4-phenylbutyl)-2-furoate (**21**, Table 2).* Following the general vinylogous aldol procedure with ATNP, compound **21** was obtained as colorless oil (0.034 g, 27% yield): R_f = 0.29 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.31−7.28 (m, 2H), 7.22−7.18 (m, 3H), 7.12 (d, J = 3.4 Hz, 1H), 6.25 (d, J = 3.4 Hz, 1H), 4.05−3.96 (br m, 1H), 3.88 (s, 3H), 2.92 (A of ABX, J = 15.1, 4.3 Hz, 1H), 2.85 (B of ABX, J = 15.1, 7.9 Hz, 1H), 2.87−2.80 (m obscured, 1H), 2.75−2.67 (m, 1H), 2.05 (br s, 1H), 1.89−1.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 157.9, 143.7, 141.8, 128.7, 128.6, 126.1, 119.5, 109.9, 69.6, 52.0, 38.7, 36.8, 32.1; IR 3449, 2946, 1718, 1518, 1437, 1309 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{18}O_4Na$ $[M + Na]^+$ 297.1103; found 297.1109.

*Methyl 5-(2-Hydroxy-2-methylbutyl)-2-furoate (**23**, Table 3).* Following the general vinylogous aldol procedure with ATNP, compound **23** was obtained as colorless oil (0.068 g, 68% yield): R_f = 0.20 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, J = 3.4 Hz, 1H), 6.28 (d, J = 3.5, 1H), 3.88 (s, 3H), 2.88 (A of AB, J = 14.7 Hz, 1H), 2.85 (B of AB, J = 14.7 Hz, 1H), 2.18 (s, 1H), 1.53 (q, J = 7.5 Hz, 2H), 1.20 (s, 3H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 157.9, 143.8, 119.5, 110.7, 73.0, 52.1, 40.5, 34.7, 26.3, 8.5; IR 3492, 2969, 1719, 1517, 1437, 1309 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{16}O_4Li$ $[M + Li]^+$ 218.1195; found 218.1196.

*Methyl 5-[4-(Benzyloxy)-2-hydroxy-2-methylbutyl]-2-furoate (**25**, Table 3).* Following the general vinylogous aldol procedure with ATNP, compound **25** was obtained as colorless oil (0.061 g, 50% yield): R_f = 0.32 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.46−7.43 (m, 2H), 7.39−7.33 (m, 2H), 7.29−7.25 (m, 1H), 7.06 (d, J = 3.4 Hz, 1H), 6.04 (d, J = 3.4 Hz, 1H), 3.88 (s, 3H), 3.23 (A of AB, J = 15.0 Hz, 1H), 3.20 (B of AB, J = 15.0 Hz, 1H), 2.18 (s, b, 1H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 157.0, 146.8, 143.5, 128.6, 128.3, 127.1, 124.7, 119.2, 110.7, 74.2, 51.9, 43.1, 29.7, 25.9; IR 3474, 2976, 1720, 1593, 1517, 1310 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{16}O_4Li$ $[M + Li]^+$ 266.1200; found 266.1199.

*Methyl 5-[4-(Benzyloxy)-2-hydroxy-2-methylbutyl]-2-furoate (**27**, Table 3).* Following the general vinylogous aldol procedure with ATNP, compound **27** was obtained as colorless oil (0.076 g, 51% yield): R_f = 0.31 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.39−7.28 (m, 5H), 7.13 (d, J = 3.4 Hz, 1H), 6.27 (d, J = 3.4 Hz, 1H), 4.53 (apparent s, 2H), 3.87 (s, 3H), 3.77 (t, J = 5.8 Hz, 2H), 2.91 (s, 2H), 1.88 (A of ABMX, J = 15.0, 4.2, 1H), 1.31 (B of ABMX, J = 15.0, 5.1, 1H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 157.9, 143.4, 137.7, 128.6, 128.0, 127.9, 119.4, 110.6, 73.6, 72.5, 67.4, 51.9, 41.4, 39.7, 27.0; IR 3485, 2949, 2869, 1720, 1593, 1517, 1454, 1310 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{22}O_5Li$ $[M + Li]^+$ 324.1618; found 324.1620.

*Methyl 5-(2-Hydroxy-2-methyl-4-phenylbutyl)-2-furoate (**29**, Table 3).* Following the general vinylogous aldol procedure with ATNP, compound **29** was obtained as pale yellow amorphous solid (0.078 g, 58% yield): R_f = 0.31 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.28 (m, 2H), 7.24−7.18 (m, 3H), 7.16 (d, J = 3.4 Hz, 1H), 6.30 (d, J = 3.4 Hz, 1H), 3.90 (s, 3H), 2.97 (A of AB, J = 14.7 Hz, 1H), 2.94 (B of AB, J = 14.7 Hz, 1H), 2.82−2.72 (m, 2H), 1.83−1.79 (m, 2H), 1.78 (s, 1H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 157.5, 144.0, 142.3, 128.7, 128.6, 126.1, 119.4, 110.8, 72.6, 52.0, 44.1, 41.0, 30.7, 27.1; IR 3466, 2950, 1720, 1517, 1436, 1310 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{20}O_4Li$ $[M + Li]^+$ 295.1516; found 295.1529.

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*4-Methyl-3-(phenylmethoxy)pentanal (**16**, Table 2).* 4-(Benzyloxy)-5-methyl-1-hexene[27] (1.95 g, 7.64 mmol, 1 equiv) was taken up in freshly distilled CH_2Cl_2 and cooled to −78 °C in a dry ice/acetone bath. A stream of ozone from an ozone generator was bubbled through for 20 min until the solution turned blue. Nitrogen was bubbled through until the blue color dissipated. Dimethylsulfide (2.82 mL, 38.2 mmol, 5 equiv) was added, and the reaction was allowed to warm to room temperature and stirred overnight. The reaction was concentrated under reduced pressure, and the crude product was purified by flash chromatography (10:1 hexanes/EtOAc). The desired product was isolated as a clear oil (1.164 g, 74% yield), which was spectroscopically identical to that reported in the literature.[28]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02473.

Copies of ^1H and ^{13}C spectra of products for the reactions described in Tables 2−4 (PDF)

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Notes

The authors declare no competing financial interest.

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