Lewis Base Activation of Lewis Acids: Vinylogous Aldol Additions of Silyl Dienol Ethers to Aldehydes

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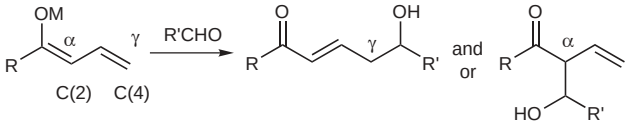
Abstract: Highly regioselective vinylogous aldol additions of silyl dienol ethers derived from simple α,β-unsaturated ketones are described. The catalyst system of silicon tetrachloride activated by chiral bisphosphoramide (*R*,*R*)-**1** effectively promotes the addition of both γ-substituted and unsubstituted silyl dienol ethers to a variety of aldehydes with exclusive γ-regioselectivity and good to excellent diastereo- and enantioselectivity.

Key words: Lewis base, asymmetric catalysis, vinylogous aldol reactions, ketones, regioselectivity

The vinylogous aldol reaction[1] has emerged as useful strategic disconnection for the stereocontrolled construction of functionalized carbon chains. This reaction has been featured in a number of recent total syntheses of natural products such as callipeltoside A[2] and leucascandrolide A.[3] This reaction involves the γ-addition of a dienol ether or ketene acetal to an aldehyde to generate an ε-hydroxyl-α,β-unsaturated carbonyl compound in which up to three stereocenters can be created. Furthermore, the newly constructed hydroxyl stereocenter adjacent to the double bond allows for stereoselective elaboration of the olefin using highly predictable substrate-controlled transformations.[4]

Although similar to simple aldol reactions,[5] the vinylogous aldol reaction overlays the challenge of regioselectivity onto the already present issues of diastereo- and enantioselectivity.[1] The addition of a dienolate to an aldehyde can generate either the α- or the γ-addition products (Scheme 1). Obtaining the γ-adduct is particularly problematic when metallo-dienolates are employed, as the inherent kinetic selectivity of these species is for reaction at the α-position, owing to the higher electron density at C(2).[6] An imaginative strategy to obtain the γ-adduct exclusively using metallo-dienolates was developed by Yamamoto and co-workers through the use of a sterically demanding Lewis acid.[7] Pre-formation of a complex between a lithium dienolate and the bulky reagent allows for steric blocking of the α-position and effectively forces the reaction to occur at the remote γ-position.



Scheme 1

An alternative strategy that allows for high γ-selectivity is the use of silyl dienolates as nucleophiles in Lewis acid-promoted vinylogous Mukaiyama-aldol additions.[8] Reactions of silyl dienol ethers are under frontier molecular orbital control whereby the higher orbital coefficient at C(4) favors the vinylogous aldol reaction.[6] Furthermore, this Lewis acid-catalyzed reaction has provided an ideal platform for development of a catalytic asymmetric variant, and several highly selective systems have been reported.[9] However, the generality of these systems is not broad as the scope of the nucleophile is limited to lactone-, dioxanone- and simple ester-derived silyl dienol ethers. More importantly, the inherent γ-selectivity of silyl dienol ethers is most often modest, particularly in the case of simple ester derived dienol ethers. A recent disclosure from these laboratories demonstrated that the combination of catalytic amounts of the chiral bis-phosphoramide (*R*,*R*)-**1**[10] and silicon tetrachloride is able to promote the addition of simple ester-derived dienol ethers to aldehydes with almost exclusive γ-regioselectivity for a variety of substitution patterns on the dienol ether while maintaining high enantio- and diastereoselectivity (Scheme 2).[11] This conceptually novel approach to carbonyl addition reactions combines the use of chiral Lewis bases to generate catalytically active chiral Lewis acids. In the presence of catalytic amounts of a chiral phosphoramide, the weak Lewis acid $SiCl_4$ can be activated to form a strongly Lewis acidic chiral species through coordination and subsequent ionization of a chloride ligand.[12] The extremely high selectivity of this catalyst system for the γ-position attests to the strong steric differentiation provided by the catalyst during the addition reaction.

With a broad scope in simple ester-derived silyl dienol ethers demonstrated, exploration into the use of new nucleophile partners has been undertaken. We report herein a catalytic enantioselective vinylogous aldol reaction for the addition of silyl dienol ethers derived from α,β-unsaturated ketones to various aldehydes.

Although the formation of cross-conjugated dienolates is overwhelmingly favored in kinetically controlled enolization, the extended conjugated dienolates of α,β-unsaturat-

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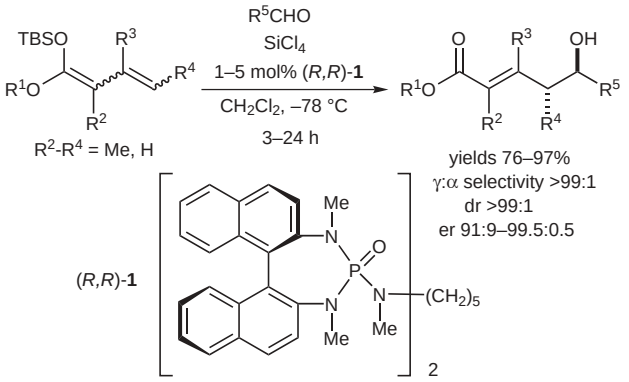
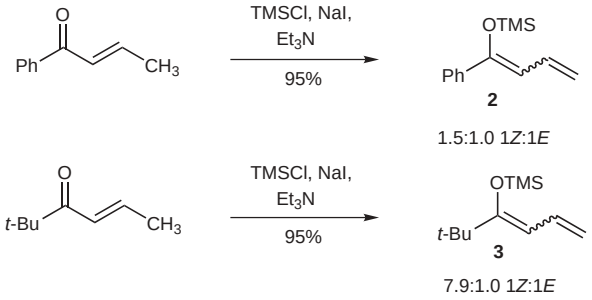


Scheme 2

ed ketones are difficult to obtain.[13] To simplify the analysis of the product mixture, α,β-unsaturated ketones lacking α′-protons were examined in this study to assure exclusive formation of fully conjugated dienolates. Trimethylsilyl enol ethers **2** and **3** were prepared following the method described by Fleming,[14] by heating the corresponding ketones in the presence of Et_3N, TMSCl, and NaI at 100 °C (Scheme 3). The dienol ethers were formed as mixtures of geometrical isomers in which the major isomer in both dienolates contains a (1*Z*)-double bond as determined by analysis of their ^{1}H NOE NMR spectra.



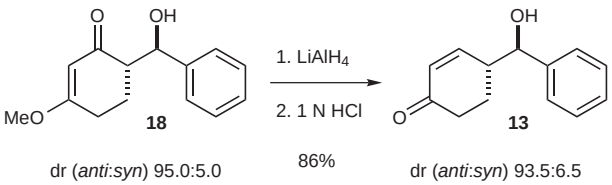
Scheme 3

Orienting experiments were conducted with dienol ether **2** and benzaldehyde under the reaction conditions developed in these laboratories for the addition of TMS enol ethers of methyl ketones to aldehydes.[15] Thus, **2** (1.2 equiv) was combined with benzaldehyde, $SiCl_4$ (1.5 equiv), *i*-Pr_2NEt (0.1 equiv) at 0.5 M in CH_2Cl_2 in the presence of 5 mol% of (*R*,*R*)-**1** at –78 °C for four hours. ^{1}H NMR analysis of the crude reaction mixture (obtained by quenching the reaction with a 1:1 mixture of sat. aq KF/sat. aq $NaHCO_3$ solutions) showed that only unreacted starting material was present. Gratifyingly, we found that by executing the reaction at an elevated temperature (–50 °C) for 24 hours, the γ-addition product could be obtained in high yield (80%), enantioselectivity (99.0:1.0 er) and exclusively of *E* configuration (Table 1, entry 1). The α-addition product could not be found by inspection of the ^{1}H NMR spectrum of the crude reaction mixture. Under these conditions, dienol ether **3** also reacted with benzaldehyde and again the γ-addition product was obtained exclusively in high yield (94%) and enantioselectivity (99.5:0.5 er).

To examine the scope of this process a number of aldehydes were surveyed in reaction with dienolate **3**. Aromatic and olefinic aldehydes reacted with excellent selectivities and yields (Table 1, entries 3 and 4). Also, heteroaromatic aldehydes are competent acceptors with only a minor decrease in selectivity (entries 5 and 6). The propargylic aldehyde, a problematic aldehyde in many addition reactions, displayed only a slightly lower selectivity (entry 7). Unfortunately, aliphatic aldehydes were found to be completely unreactive with dienolate **3** (entry 8). Even warming of the reaction temperature to 0 °C did not allow for the formation of a vinylogous aldol product. Remarkably, only the γ-addition product could be observed by ^{1}H NMR analysis of the crude reaction mixture in all of the aldehydes that reacted.

In view of the high selectivity observed in the addition of γ-unsubstituted enones to aldehydes, cyclic dienolate **12**[16] was investigated to evaluate diastereoselectivity as well as enantio- and regioselectivity. Initial studies showed that when **12** (1.2 equiv) was combined with benzaldehyde, $SiCl_4$ (1.5 equiv), *i*-Pr_2NEt (0.1 equiv) at 0.5 M in CH_2Cl_2 in the presence of 5 mol% of (*R*,*R*)-**1** at –78 °C for 2 hours, the γ-addition product could be obtained exclusively with excellent *anti* diastereoselectivity (97.5:2.5) and enantioselectivity (97.5:2.5; Table 2, entry 1). Exclusive γ-regioselectivity was also observed in the addition of dienolate **12** to 1-naphthaldehyde; however, increasing the reaction time to 10 hours was required to obtain high yields (Table 2, entry 2). Although the diastereoselectivity was attenuated (89.0:11.0), both the *anti* and *syn* diastereomers were formed with high enantioselectivity (95.0:5.0 and >99.5:0.5, respectively). Reactions with cinnamaldehyde and 2-furaldehyde provided the γ-addition products in high yield with excellent *anti* diastereoselectivity and good enantioselectivity (entries 3 and 4). Despite several attempts, dienol ether **12** did not react with aliphatic aldehydes (entry 5).

The *anti*-configuration of the major diastereomer was unambiguously assigned by an independent synthesis of cyclohexenone **13**. A diastereomerically enriched (*anti*/*syn* 95:5) sample of the 3-methoxy-1′-hydroxy ketone **18**[17] was prepared. Reduction ($LiAlH_4$) of **18** followed by acidic hydrolysis afforded 2-cyclohexenone **13** as a 93.5:6.5 mixture of diastereomers (Scheme 4). Comparison of their ^{1}H NMR spectra allowed the assignment of the major diastereomers from the reaction of **12** as *anti*.



Scheme 4

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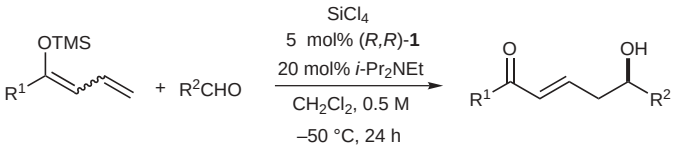
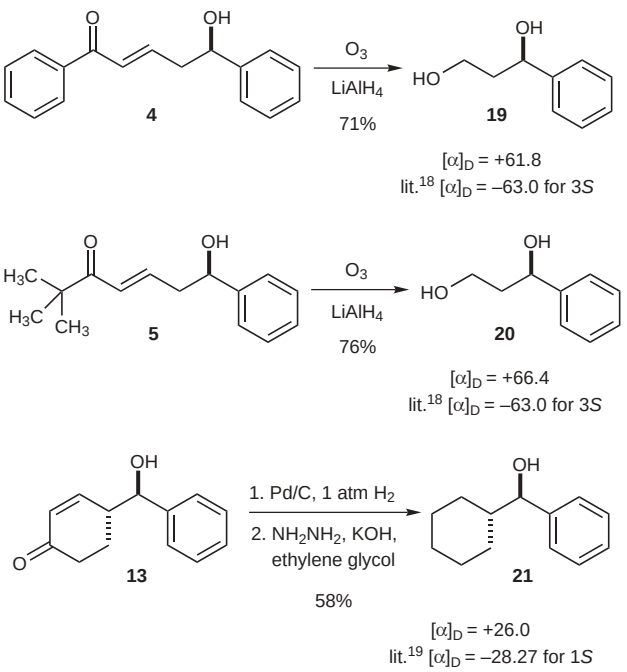
Table 1 Vinylogous Aldol Reactions of Ketone-Derived Dienolate **2** and **3** with Aldehydes[a]



Entry	Dienolate	R^1	R^2	Product	Yield (%)[b]	λ/α[c]	er[d]
1	**2**	Ph	Ph	**4**	80	>99:1	99.0:1.0
2	**3**	*t*-Bu	Ph	**5**	94	>99:1	99.5:0.5
3	**3**	*t*-Bu	1-Naphthyl	**6**	85	>99:1	99.0:1.0
4	**3**	*t*-Bu	(*E*)-PhCH=CH	**7**	82	>99:1	>99.5:0.5
5	**3**	*t*-Bu	2-Furyl	**8**	90	>99:1	96.0:4.0
6[e]	**3**	*t*-Bu	2-Thienyl	**9**	50[f]	>99:1	94.0:6.0
t[g]	**3**	*t*-Bu	PhC≡C	**10**	40[f]	>99:1	84.0:16.0
8	**3**	*t*-Bu	$PhCH_2CH_2$	**11**	0	Nd[h]	Nd

[a] Reactions employed 1.5 equiv of $SiCl_4$, 1.2 equiv of dienolate, 0.2 equiv of *i*-Pr_2NEt, 0.05 equiv of (*R*,*R*)-**3** at 0.5 M in CH_2Cl_2 at –50 °C for 24 h.
[b] Yields of analytically pure material.
[c] Determined by ^1H NMR analysis.
[d] Determined by CSP-SFC.
[e] Conditions as above with 0.1 equiv of (*R*,*R*)-**1**.
[f] Yield after chromatography.
[g] Conditions as above with 0.1 equiv of (*R*,*R*)-**1** and at –68 °C.
[h] Nd: not determined.

To establish the absolute configuration of the adducts, compounds **4** and **5** were subjected to ozonolysis followed by reduction of the ozonide with a solution of lithium aluminum hydride which afforded the desired diols in good yields (Scheme 5). Comparison of their optical rotations with those reported in the literature[18] showed that the major enantiomer in both cases was the aldol adduct derived from *Re* face attack on the aldehyde. In the case of aldol adduct **13**, correlation to the known 1-cyclohexyl-1-phenylmethanol was made by hydrogenation of the double bond in **13** followed by Wolff–Kishner reduction (Scheme 5). Comparison of the optical rotation of **21** to that in the literature shows that the C(1) center is of *R*-configuration. Thus, the *anti* relationship between the two stereocenters in adduct **13** allows for assignment of the absolute configuration of the major enantiomer as (4*R*,7*R*)-**13**. In all cases, the sense of asymmetric induction is consistent with that observed in all other reported cases employing chiral bisphosphoramide (*R*,*R*)-**1** and $SiCl_4$.



Scheme 5

To the best of our knowledge, these findings represent the first catalytic and enantioselective vinylogous aldol reaction that employ silyl dienol ethers derived from simple α,β-unsaturated ketones. These reactions proceed with exclusive γ-selectivity and high enantioselectivity and diastereoselectivity in the addition to aromatic, heteroaromatic, olefinic, and propargylic aldehydes. Current studies are underway to overcome the lack of reactivity with aliphatic aldehydes and extend this methodology to acyclic α′-enolizable ketones.

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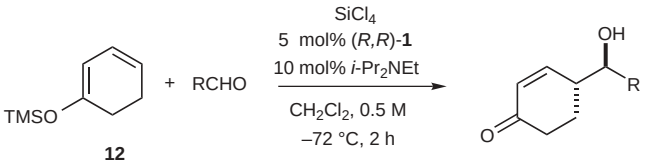
Table 2 Vinylogous Aldol Reactions of Ketone-Derived Dienolate **12** with Aldehydes[a]



12

Entry	R^1	Product	Yield (%)[b]	γ/α[c]	dr (*anti*/*syn*)[d]	er *anti*[d]	er *syn*[d]
1	Ph	**13**	90[e]	>99:1	97.5:2.5	97.5:2.5	Nd
2[f]	1-Naphthyl	**14**	80[e]	>99:1	89.0:11.0	95.0:5.0	>99.5:0.5
3	(*E*)-PhCH=CH	**15**	74	>99:1	98.0:2.0	84.5:15.5	Nd
4	2-Furyl	**16**	94	>99:1	95.5:4.5	81.5:18.5	Nd
5	$PhCH_2CH_2$	**17**	0	Nd[g]	Nd	Nd	Nd

[a] Reactions employed 1.5 equiv of $SiCl_4$, 1.2 equiv of dienolate, 0.1 equiv of *i*-Pr_2NEt, 0.05 equiv of (*R*,*R*)-**1** at 0.5 M in CH_2Cl_2 at –72 °C for 2 h.
[b] Yields of analytically pure material.
[c] Determined by ^1H NMR analysis.
[d] Determined by CSP-SFC.
[e] Yield after chromatography.
[f] Conditions as above for 10 h.
[g] Nd: not determined.

General Procedure for the Aldol Reaction of 2.

(+)-(*R*)-5-Hydroxy-1,5-diphenyl-2-penten-1-one (4).

Di*iso*propylethylamine (35 μL, 0.2 mmol, 0.2 equiv) was added via syringe to a flame-dried, 5 mL, Schlenk flask under Ar containing a solution of 42 mg (0.05 mmol, 0.05 equiv) of *bis*-phosphoramide (*R*,*R*)-**1** in CH_2Cl_2 (2 mL). To this solution was added 102 μL (1.0 mmol) of benzaldehyde in one portion. To the resulting solution was added 172 μL (1.5 mmol, 1.5 equiv) of $SiCl_4$ in one portion. To the resulting solution was added 172 μL (1.5 mmol, 1.5 equiv) of $SiCl_4$ in one portion and the reaction mixture was cooled to –50 °C over 15 min. Then, 284 μL (1.2 mmol, 1.2 equiv) of **2** was added dropwise over 1 min. The resulting mixture was stirred at –50 °C for 24 h whereupon 3 mL of chilled CH_2Cl_2 was added before the cold reaction mixture was poured into a rapidly stirring solution of 1:1 sat. aq $NaHCO_3$/sat. aq KF (25 mL) at 0 °C. This biphasic mixture was stirred vigorously for 1 h before being filtered through Celite. The phases were then separated and the aqueous layer was washed with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 4:1) to give 201 mg (80%) of (+)-**4** as thick oil, which solidified upon standing. Data for **4**: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 7.1 Hz, 2 H), 7.55 (dt, *J* = 7.5, 1.5 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.39–7.35 (m, 4 H), 7.32–7.28 (m, 1 H), 7.06–7.00 (m, 1 H), 6.91 (dt, *J* = 15.4, 1.3 Hz, 1 H), 4.90 (dd, *J* = 7.7, 5.1 Hz, 1 H), 2.83–2.71 (m, 2 H), 2.31 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.71, 144.99, 143.47, 137.62, 132.77, 128.63, 128.60, 128.55, 128.51, 127.92, 125.75, 73.15, 42.45. $[\alpha]_D^{24}$ +14.40 (*c* 1.00, EtOH). SFC: (*R*)-**4** t_R 3.04 min (99.0%); (*S*)-**4** t_R 4.06 min (1.0%) (AD column, 175 bar, 3.0 mL/min, 20.0% MeOH). Anal. Calcd for $C_{17}H_{16}O_2$ (252.31): C, 80.93%; H, 6.39%. Found: C, 80.63%; H, 6.33%.

(+)-(*R*)-7-Hydroxy-2,2-dimethyl-7-phenyl-4-hepten-3-one (5).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 6.94–6.88 (m, 1 H), 6.53 (dt, *J* = 15.3, 1.4 Hz, 1 H), 4.84 (dd, *J* = 7.6, 5.4 Hz, 1 H), 2.72–2.61 (m, 2 H), 2.02 (br s, 1 H), 1.11 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.17, 143.47, 142.56, 128.55, 127.83, 127.03, 125.76, 73.14, 42.80, 42.18, 26.03. $[\alpha]_D^{24}$ +6.12 (*c* 0.95, EtOH). SFC: (*R*)-**5** t_R 5.63 min (99.5%); (*S*)-**5** t_R 6.41 min (0.5%) (AD column, 150 bar, 3.0 mL/min, 3.5% MeOH). Anal. Calcd for $C_{15}H_{20}O_2$ (232.32): C, 77.55%; H, 8.68%. Found: C, 77.58%; H, 8.72%.

(+)-(*R*)-7-Hydroxy-2,2-dimethyl-7-(1-naphthalenyl)-4-hepten-3-one (6).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.3 Hz, 1 H), 7.89 (d, *J* = 8.8 Hz, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 7.67 (d, *J* = 7.1 Hz, 1 H), 7.56–7.47 (m, 3 H), 7.08–7.02 (m, 1 H), 6.57 (dd, *J* = 15.3, 1.4 Hz, 1 H), 5.64 (dd, *J* = 8.0, 4.4 Hz, 1 H), 2.92–2.75 (m, 2 H), 2.11 (br s, 1 H), 1.11 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.33, 143.11, 139.10, 133.73, 130.04, 128.96, 128.29, 128.12, 126.77, 126.11, 125.54, 125.40, 122.93, 122.79, 69.74, 42.76, 41.22, 26.00. $[\alpha]_D^{24}$ +57.11 (*c* 1.10, EtOH). SFC: (*S*)-**6** t_R 3.59 min (1.0%); t_R (*R*)-**6** 4.81 min (99.0%) (OD column, 125 bar, 3.0 mL/min, 17.5% MeOH). Anal. Calcd for $C_{19}H_{22}O_2$ (282.38): C, 80.82%; H, 7.85%. Found: C, 80.70%; H, 7.83%.

(–)-(*R*)-7-Hydroxy-2,2-dimethyl-9-phenyl-4,8-nonadien-3-one (7).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.1 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 7.27–7.24 (m, 1 H), 6.96 (dt, *J* = 15.1, 7.6 Hz, 1 H), 6.64–6.60 (m, 2 H), 6.23 (dd, *J* = 15.9, 6.6 Hz, 1 H), 4.84 (dd, *J* = 7.6, 5.4 Hz, 1 H), 2.56 (t, *J* = 7.1 Hz, 2 H), 1.82 (br s, 1 H), 1.15 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.14, 142.37, 136.34, 131.02, 130.93, 128.60, 127.85, 127.08, 126.52, 71.53, 42.84, 40.47, 26.07. $[\alpha]_D^{24}$ –27.42 (*c* 0.90, EtOH). SFC: (*R*)-**7** t_R 2.93 min (>99.5%); (*S*)-**7** t_R 3.62 min (<0.5%) (OD column, 125 bar, 3.0 mL/min, 15.0% MeOH). Anal. Calcd for $C_{17}H_{22}O_2$ (258.36): C, 79.03%; H, 8.58%. Found: C, 79.00%; H, 8.71%.

(+)-(*R*)-7-Hydroxy-2,2-dimethyl-7-(2-furanyl)-4-hepten-3-one (8).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 1.7, 0.9 Hz, 1 H), 6.89 (dt, *J* = 15.4, 7.5 Hz, 1 H), 6.58 (dt, *J* = 15.3,1.3 Hz, 1 H), 6.33 (dd, *J* = 3.2, 1.7 Hz, 1 H), 6.26 (d, *J* = 3.2 Hz, 1 H), 4.85 (t, *J* = 6.6 Hz, 1 H), 2.80–2.76 (m, 2 H), 2.02 (br s, 1 H), 1.13 (s, 9 H). ^{13}C

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NMR (125 MHz, $CDCl_3$): δ = 204.09, 155.41, 142.20, 141.71, 127.12, 110.24, 106.48, 66.54, 42.84, 38.54, 26.03. $[\alpha]_D^{24}$ +3.80° (*c* 1.0, EtOH). SFC: (*R*)-**7** t_R 5.73 min (96.0%); (*S*)-**7** t_R 6.63 min (4.0%) (AD column, 150 bar, 3.0 mL/min, 2.5% MeOH). Anal. Calcd for $C_{13}H_{18}O_3$ (222.28): C, 79.24%; H, 8.16%. Found: C, 69.89%; H, 8.20%.

(–)-(*R*)-7-Hydroxy-2,2-dimethyl-7-(2-thienyl)-4-hepten-3-one (9).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.25 (m, 1 H), 6.99–6.93 (m, 2 H), 6.89 (dt, *J* = 15.4, 7.4 Hz, 1 H), 6.58 (dt, *J* = 15.1, 1.5 Hz, 1 H), 5.09 (dd, *J* = 7.0, 6.1 Hz, 1 H), 2.82–2.71 (m, 2 H), 2.12 (br s, 1 H), 1.13 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.25, 147.35, 141.92, 127.21, 126.68, 124.79, 123.97, 66.98, 42.83, 42.21, 26.00. $[\alpha]_D^{24}$ –5.26 (*c* 1.00, EtOH). SFC: (*R*)-**7** t_R 5.63 min (94.0%); (*S*)-**7** t_R 6.63 min (4.0%) (AD column, 125 bar, 2.75 mL/min, 5.0% MeOH). Anal. Calcd for $C_{13}H_{18}O_2S_1$ (238.35): C, 65.51%; H, 7.61%. Found: C, 65.30%; H, 7.66%.

(–)-(*R*)-7-Hydroxy-2,2-dimethyl-9-phenyl-4-nonen-8-yn-3-one (10).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.41 (m, 2 H), 7.35–7.29 (m, 3 H), 7.02 (dt, *J* = 15.4, 7.5 Hz, 1 H), 6.69 (dt, *J* = 15.4, 1.2 Hz, 1 H), 4.75 (t, *J* = 6.1 Hz, 1 H), 2.73 (dt, *J* = 6.1, 1.2 Hz, 2 H), 1.65 (br s, 1 H), 1.16 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.08, 141.11, 131.70, 128.61, 128.30, 127.52, 122.20, 88.76, 85.84, 61.63, 42.89, 40.72, 26.07. $[\alpha]_D^{24}$ –15.96 (*c* 0.99, EtOH). SFC: (*R*)-**7** t_R 1.90 min (84.0%); (*S*)-**7** t_R 3.60 min (16.0%) (OD column, 125 bar, 3.00 mL/min, 17.5% MeOH). Anal. Calcd for $C_{17}H_{20}O_2$ (256.34): C, 79.65%; H, 7.86%. Found: C, 79.68%; H, 7.72%.

General Procedure for the Aldol Reaction of 12. (+)-(4*R*,7*R*)-4-(Hydroxyphenylmethyl)-2-cyclohexen-1-one (*anti*-13).

Di*iso*propylethylamine (18 μL, 0.1 mmol, 0.1 equiv) was added via syringe to a flame-dried, 5 mL, Schlenk flask under N_2 containing a solution of 42 mg (0.05 mmol, 0.05 equiv) of *bis*-phosphoramide (*R*,*R*)-**1** in CH_2Cl_2 (2 mL). To this solution was added 102 μL (1.0 mmol) of benzaldehyde in one portion. To the resulting solution was added 172 μL (1.5 mmol, 1.5 equiv) of $SiCl_4$ in one portion and the reaction mixture was cooled to –72 °C over 15 min. Then, 224 μL (1.2 mmol, 1.2 equiv) of **12** was added dropwise over 1 min. The resulting mixture was stirred at –72 °C for 2 h whereupon 3 mL of chilled CH_2Cl_2 was added before the cold reaction mixture was poured into a rapidly stirring solution of 1:1 sat. aq $NaHCO_3$/sat. aq KF (25 mL) at 0 °C. This biphasic mixture was stirred vigorously for 1 h before being filtered through Celite. The phases were then separated and the aqueous layer was washed with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, pentane–Et_2O, 1:1) to give 182 mg (90%) of (+)-**13**[7a] as thick oil, which solidified upon standing. Data for (*anti*-**13**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.32 (m, 5 H), 7.25 (dt, *J* = 10.3, 1.7 Hz, 1 H), 6.09 (dd, *J* = 10.3, 2.4 Hz, 1 H), 4.59 (dd, *J* = 7.8, 3.2 Hz, 1 H), 2.78–2.73 (m, 1 H), 2.49–2.21 (m, 1 H), 2.35–2.28 (m, 1 H), 2.03 (br s, 1 H), 1.75–1.68 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.95, 151.63, 142.17, 129.83, 128.62, 128.142, 126.24, 76.54, 43.58, 36.74, 25.82. $[\alpha]_D^{24}$ +114.38 (*c* 1.00, EtOH). SFC: (4*S*,7*S*)-**13** t_R 6.52 min (2.5%); (4*R*,7*R*)-**13** t_R 9.65 min (97.5%) (OJ column, 150 bar, 2.75 mL/min, 6.0% MeOH).

(+)-(4*R*,7*R*)-4-[Hydroxy-(1-naphthalenyl)methyl]-2-cyclohexen-1-one (*anti*-15).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.3 Hz, 1 H), 7.91 (d, *J* = 9.3 Hz, 1 H), 7.84 (d, *J* = 8.3 Hz, 1 H), 7.68 (d, *J* = 7.1 Hz, 1 H), 7.57–7.50 (m, 3 H), 7.23 (dt, *J* = 10.3, 1.8 Hz, 1 H), 6.08 (dd, *J* = 10.3, 2.2 Hz, 1 H), 5.38 (d, *J* = 6.6 Hz, 1 H), 3.06–3.01 (m, 1 H), 2.48 (dt, *J* = 16.8, 4.2 Hz, 1 H), 2.23 (ddd, *J* = 16.8, 13.4, 5.1 Hz, 1 H), 2.21 (br s, 1 H), 1.99–1.91 (m, 1 H), 1.84–1.80 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.04, 151.43, 137.77, 133.83, 130.36, 129.83, 129.08, 128.50, 126.23, 125.70, 125.33, 125.25, 124.01, 122.86, 73.35, 42.77, 36.87, 26.51. $[\alpha]_D^{24}$ +89.08 (*c* 0.90, EtOH). SFC: (4*S*,7*S*)-**15** t_R 2.50 min (5.0%); (4*R*,7*R*)-**15** t_R 5.08 min (95.0%) (OJ column, 150 bar, 4.0 mL/min, 20.0% MeOH). HRMS (ES+) *m*/*z* calcd for $C_{17}H_{17}O_2$: 253.1229; found: 253.1244.

(+)-(4*R*,7*R*)-4-[Hydroxy-(3-phenylpropenyl)]-2-cyclohexen-1-one (*anti*-16).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7.8 Hz, 2 H), 7.34 (t, *J* = 7.3 Hz, 2 H), 7.30–7.27 (m, *J* = 7.3, 1.2 Hz, 1 H), 7.16 (ddd, *J* = 10.3, 2.3, 1.6 Hz, 1 H), 6.67 (d, *J* = 15.9 Hz, 1 H), 6.26 (dd, *J* = 15.9, 6.8 Hz, 1 H), 6.10 (ddd, *J* = 10.3, 2.4, 0.7 Hz, 1 H), 4.23 (t, *J* = 6.8 Hz, 1 H), 2.69–2.63 (m, 1 H), 2.55 (dt, *J* = 16.8, 4.2 Hz, 1 H), 2.39 (ddd, *J* = 16.8, 13.2, 5.0 Hz, 1 H), 2.14–2.08 (m, 1 H), 1.90–1.82 (m, 1 H), 1.71 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.84, 151.13, 136.00, 132.27, 130.19, 129.56, 128.66, 128.08, 126.51, 75.04, 42.25, 36.86, 25.47. $[\alpha]_D^{24}$ +52.73 (*c* 1.43, EtOH). SFC: (4*R*,7*R*)-**16** t_R 4.91 min (84.5%); (4*S*,7*S*)-**16** t_R 6.47 min (15.5%) (OD column, 125 bar, 3.0 mL/min, 20.0% MeOH). Anal. Calcd for $C_{15}H_{16}O_2$ (228.29): C, 78.92%; H, 7.06%. Found: C, 79.03%; H, 7.06%.

(+)-(4*R*,7*R*)-4-[Hydroxy-(2-furanyl)methyl]-2-cyclohexen-1-one (*anti*-17).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (t, *J* = 1.5 Hz, 2 H), 7.35 (t, *J* = 2.0 Hz, 1 H), 6.38 (dd, *J* = 3.2, 2.0 Hz, 1 H), 6.33 (d, *J* = 3.2 Hz, 1 H), 6.10 (dd, *J* = 10.3, 2.4 Hz, 1 H), 4.64 (dd, *J* = 7.5, 5.0 Hz, 1 H), 2.98–2.94 (m, 1 H), 2.51 (dt, *J* = 16.8, 4.4 Hz, 1 H), 2.38 (ddd, *J* = 16.8, 12.9, 5.1 Hz, 1 H), 2.03 (d, *J* = 5.1 Hz, 1 H), 1.90–1.74 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.84, 154.36, 151.05, 142.43, 130.17, 110.29, 107.47, 70.13, 41.49, 36.73, 25.40. $[\alpha]_D^{24}$ +58.18 (*c* = 1.05, EtOH). SFC: (4*S*,7*S*)-**17** t_R 5.77 min (18.5%); (4*R*,7*R*)-**17** t_R 7.14 min (81.5%) (OJ column, 125 bar, 2.5 mL/min, 5.0% MeOH). Anal. Calcd for $C_{11}H_{12}O_3$ (192.21): C, 68.74%; H, 6.29%. Found: C, 68.59%; H, 6.34%.

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