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Asymmetric Synthesis of 2-Substituted Oxetan-3-ones via Metalated SAMP/RAMP Hydrazones

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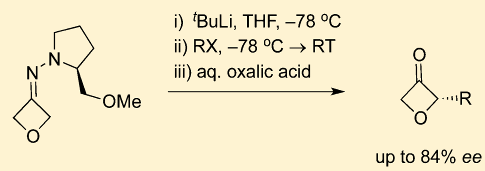
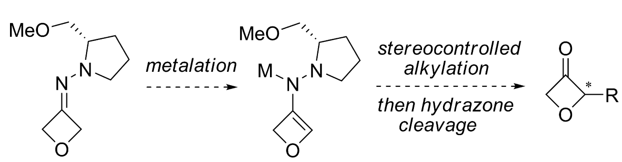
Supporting Information

ABSTRACT: 2-Substituted oxetan-3-ones can be prepared in good yields and enantioselectivities (up to 84% ee) by the metalation of the SAMP/RAMP hydrazones of oxetan-3-one, followed by reaction with a range of electrophiles that include alkyl, allyl, and benzyl halides. Additionally, both chiral 2,2- and 2,4-disubstituted oxetan-3-ones can be made in high ee (86−90%) by repetition of this lithiation/alkylation sequence under appropriately controlled conditions. Hydrolysis of the resultant hydrazones with aqueous oxalic acid provides the 2-substituted oxetan-3-ones without detectable racemization.



There is considerable current interest in the preparation of oxetanes for use in medicinal chemistry.[1,2] As a result of the pioneering work of Carreira and Rogers-Evans,[1] these 4-membered oxygen heterocycles are increasingly being used as bioisosteric replacements for common functional groups such as *gem*-dimethyl or carbonyl groups.[2] Their introduction can induce profoundly beneficial effects on the aqueous solubility, lipophilicity, metabolic stability, and conformational preference of drug candidates. To date, most work has centered on the use of oxetanes devoid of substituents at C-2 and/or C-4 to avoid the introduction of additional stereocenters into the molecular scaffold.[3] In part, this is due to the limited number of methods for the synthesis of chiral, nonracemic oxetane derivatives.[4,5] In seeking to expand the number of readily accessible, chiral oxetane building blocks, we decided to explore the enantioselective synthesis of 2-substituted oxetan-3-ones using the SAMP/RAMP hydrazone methodology developed by Enders.[6] No general asymmetric route to this oxetane subclass has been established. However, Zhang has reported a single example of a Au-catalyzed oxidative cyclization of a chiral propargylic alcohol to the enantiomerically enriched 2-substituted oxetan-3-one without racemization,[5c] and Williams has produced an enantiomerically enriched 2,2,4-trisubstituted oxetan-3-one by DMDO epoxidation/rearrangement of a chiral allene.[4a] Our proposed strategy is depicted in Scheme 1. At the outset of this study, it was unclear whether the high degree of ring strain within the metalated hydrazone intermediate might inhibit its formation. Indeed, as far as we are aware, there are no reports of enolate generation from oxetan-3-ones.[7] We were encouraged, however, by a report by Fadel and co-workers who have demonstrated that the SAMP/RAMP hydrazones of cyclobutanone can be successfully lithiated and alkylated.[8] In this paper, we demonstrate how a variety of chiral 2-substituted as well as 2,2- and 2,4-disubstituted oxetan-3-ones can be prepared by metalation/alkylation of the SAMP/RAMP hydrazones derived from oxetan-3-one, offering a practical route to these important medicinal chemistry building blocks.

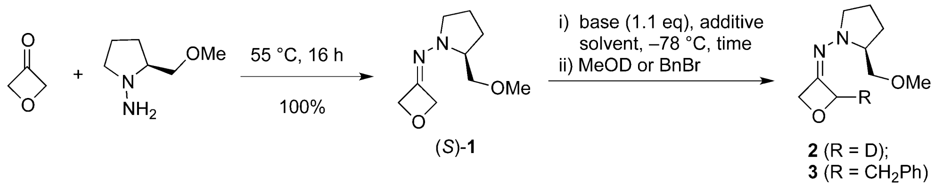
Scheme 1. Proposed Route to Chiral 2-Substituted Oxetan-3-ones



The SAMP hydrazone (*S*)-**1** was prepared in quantitative yield by treatment of SAMP with an excess of commercially available oxetan-3-one at 55 °C without solvent (Table 1). The corresponding (*R*)-enantiomer was made using RAMP in an identical fashion. In order to investigate the metalation of (*S*)-**1**, a screening of lithium bases was performed. Hydrazone (*S*)-**1** was in turn treated with 1.1 equiv of LDA, ^{n}BuLi, and ^{t}BuLi and then quenched with deuterated methanol. The extent of deuterium incorporation into **2** was estimated by mass spectrometry. Use of LDA was found to give only 59% deuterium incorporation (entry 1, Table 1), whereas ^{n}BuLi and ^{t}BuLi proved to be more effective in forming the lithiated derivative with 90% deuterium incorporation in each case (entries 2 and 3). Having identified ^{n}BuLi and ^{t}BuLi as the most suitable bases for the metalation step, alkylation with a representative carbon-based electrophile, namely benzyl bromide, was explored. After deprotonation with ^{n}BuLi at −78 °C, and subsequent trapping with this electrophile at the same temperature, the benzylated hydrazone **3** was obtained in an encouraging 45% yield (entry 4). Addition of the additive TMEDA did not lead to an improvement in yield (entry 5), and a change from THF to diethyl ether as the solvent resulted in no product formation (entry 6). Use of the stronger base ^{t}BuLi led to a higher yield (entry 7), with a modest additional improvement seen using a longer metalation time (entry 8).

Received: September 14, 2013
Published: October 23, 2013

Table 1. Optimization of Conditions for Metalation/Alkylation of SAMP Hydrazone (*S*)-1



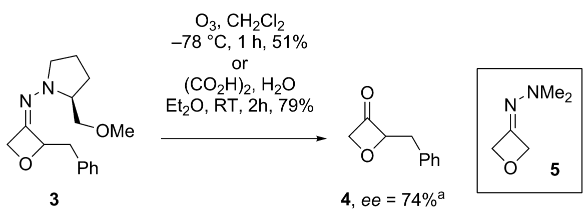
entry	base	additive	solvent	time (h)	product	conversion to **2** (%)/yield of **3** (%)
1	LDA		THF	2	**2**	59[a]
2	^{n}BuLi		THF	1	**2**	90[a]
3	^{t}BuLi		THF	1	**2**	90[a]
4	^{n}BuLi		THF	1	**3**	45[b]
5	^{n}BuLi	TMEDA	THF	1	**3**	45[b]
6	^{n}BuLi		Et_2O	1	**3**	0[b]
7	^{t}BuLi		THF	1	**3**	67[b]
8	^{t}BuLi		THF	2	**3**	73[b]

[a]Determined by mass spectrometry. [b]Isolated yield after chromatography.

Under these conditions, **3** was produced in 73% yield and 76% de (entry 8).[9] The alkylation conditions used in entry 8 were used in all subsequent studies.

Conversion of hydrazone **3** to enantiomerically enriched ketone **4** could be achieved by oxidation with ozone[10] or by hydrolysis with oxalic acid,[11] although the latter method was found to be both higher yielding and more convenient (Scheme 2). Initial attempts to determine the enantiopurity of the resulting ketone using chiral shift reagents, chiral HPLC, and chiral GC all proved unsuccessful. However, reduction of ketone **4** to the corresponding alcohol and further acetylation enabled determination of its enantiopurity by chiral GC analysis, and an ee of 74% was established (see the Supporting Information).[12] The racemic ketone **4** was prepared for comparative purposes from achiral hydrazone **5** using the same chemistry (Scheme 2).[13]

Scheme 2. Synthesis of Enantiomerically Enriched 2-Benzyloxetan-3-one (4)[a]

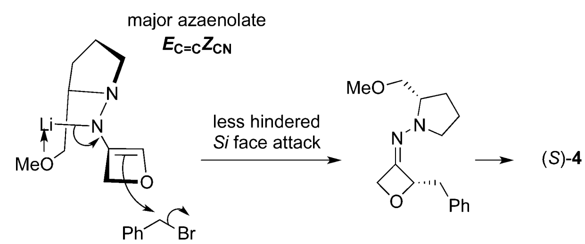


[a]ee determined by chiral GC analysis of acetates formed by $NaBH_4$ reduction and then acetylation of enantiomerically enriched and racemic ketone **4** (see the Supporting Information).

The absolute configuration of the major enantiomer derived from (*S*)-**1** was established by performing a Pictet–Spengler reaction on ketone **4** with L-tryptophan ethyl ester, using reaction conditions developed within our group (Scheme 3).[14] Two diastereoisomers, **6** and **7**, were isolated from the reaction mixture in 67% and 9% yields respectively. The structures of both **6** and **7**, and the (*S*)-configuration of the oxetane C2 stereocenter of the major product **6** were unambiguously determined by X-ray crystallography (see the Supporting Information). Importantly, the product ratio (**6**:**7**; 88:12) is in close agreement with the enantiomeric ratio (er = 87:13) of **4** determined by GC analysis, supporting the supposition that no epimerization occurs during the Pictet–Spengler cyclization.

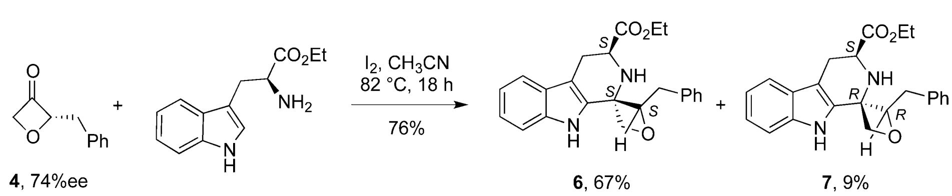
The stereochemical outcome of the alkylation of SAMP hydrazone (*S*)-**1** is in accordance with previous studies by Enders et al. and can be explained by preferential attack of a conformationally rigid and chelated $E_{C=C}Z_{C-N}$ azaenolate by the electrophile from the less sterically hindered *Si* face (Scheme 4).[8,15] The sense of asymmetric induction in the other alkylations reported herein was made by analogy.

Scheme 4. Proposed Mechanism of Formation of Major Enantiomer of 4



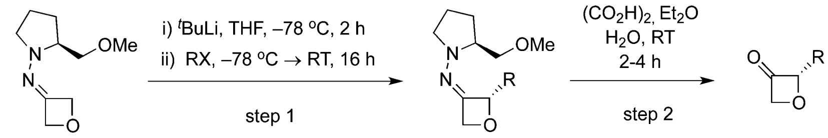
Having established satisfactory yields for both the alkylation of SAMP hydrazone (*S*)-**1** and the hydrolysis of **3** to 2-benzyloxetan-3-one (**4**), we sought to establish the scope and stereoselectivity of the alkylation step. A representative range of

Scheme 3. Determination of Absolute Configuration via Pictet Spengler Reaction

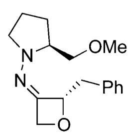
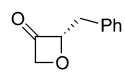
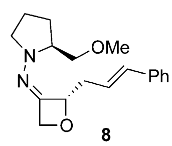
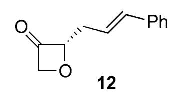
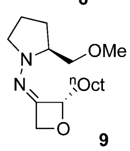
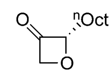
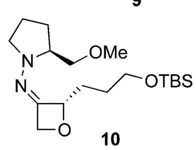
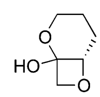
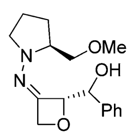
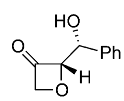
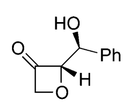


dx.doi.org/10.1021/jo4020485 | J. Org. Chem. 2013, 78, 12243−12250

Table 2. Stereoselective Synthesis of 2-Substituted Oxetan-3-ones



(*S*)-**1** **3, 8-11** **4, 12-15**

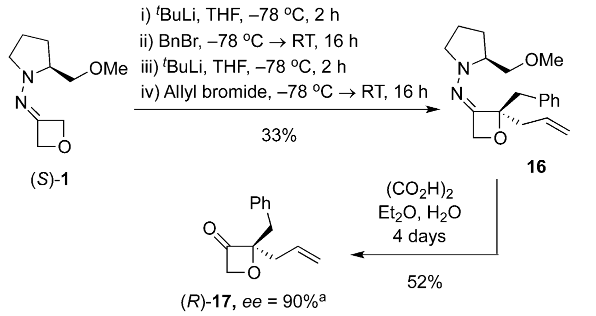
entry	electrophile (RX)	product step 1	yield step 1 (%)	product(s) step 2	yield(s) step 2 (%)	*ee* (%)
1	BnBr	 **3**	73	 **4**	79	74[a]
2	$BrCH_2CH=CHPh$	 **8**	57	 **12**	77	84[a]
3	^{n}OctI	 **9**	60	 **13**	85	83[a]
4	$ICH_2CH_2CH_2OTBS$	 **10**	68	 **14**	60	84[b]
5	PhCHO	 **11**	62	 **15a**	47	54[c]
				 **15b**	45	2[c]

[a]ee determined by chiral GC analysis of acetates formed by $NaBH_4$ reduction and then acetylation of the resulting mixture of alcohols. [b]ee determined by chiral GC analysis of enantiomerically enriched monocyclic acetate formed by acetylation of **14**. [c]ee determined by chiral GC analysis. [d]In all cases, racemic samples were prepared from achiral hydrazone **5** for comparison purposes. [e]See the Supporting Information for GC conditions and chromatograms.

electrophiles including alkyl iodides, allyl bromides, and an aldehyde were screened (Table 2). Satisfyingly, in addition to benzyl bromide, both alkyl iodides and allyl bromides were found to react in both good yield and stereoselectivity (up to 84% ee) (entries 2–5). Interestingly, treatment of **10** with oxalic acid was found to lead to both hydrazone hydrolysis and TBS removal to give bicyclic hemiketal **14** (entry 4). Although benzaldehyde reacted in good yield with the lithiated SAMP hydrazone to give **11**, the *β*-hydroxy ketones **15a** and **15b** formed on hydrolysis were found to have significantly different levels of enantiopurity (**15a**: 54% ee; **15b**, 2% ee), and the dr for **15a**:**15b** was found to be essentially 1:1 by ^1H NMR (entry 5). The relative stereochemistry within both **15a** and **15b** was established by X-ray crystallography (see the Supporting Information). The poorer facial selectivity seen in this reaction may be attributed to a breakdown in the coordination of the methoxy group of the chiral auxiliary to the lithium azaenolate due to competing coordination by the aldehyde oxygen.[16] Good selectivities for the aldol reaction of lithiated cyclic SAMP hydrazones have only been reported for much bulkier aldehydes which are less likely to affect lithium coordination within the auxiliary.[17]

Having achieved good yields and selectivities for the monoalkylation of (*S*)-**1** in the majority of cases, we next explored the feasibility of making disubstituted oxetan-3-one derivatives using this methodology. By treating (*S*)-**1** sequentially with ^{t}BuLi, benzyl bromide, ^{t}BuLi, and allyl bromide in one-pot, 2,2-dialkylated hydrazone **16** was isolated in 33% yield (Scheme 5). Hydrazone cleavage provided ketone **17** in excellent enantiopurity (90% ee). As before, the ee was determined by GC analysis of acetate derivatives (see the Supporting Information). In this case, however, we were unable to prepare racemic ketone **17** from dimethyl hydrazone **5** so instead prepared the opposite enantiomer of **17** from RAMP-derived hydrazone (*R*)-**1** for comparison purposes. While the generation of a quaternary stereocenter at the α-position of a SAMP/RAMP hydrazone is known,[18] this is, to the best of our knowledge, the first example of the generation of a quaternary center from an α-CH_2 unit where there is no prior monoalkylation observed at the α'-CH_2 unit. The high activation energy for conversion of the (*Z*)-2-benzyl hydrazone **3** (formed from the first alkylation) to the corresponding (*E*)-hydrazone explains the lack of α'-alkylation in this case.[19] One explanation for the higher enantioselectivity seen in the formation of **17** compared with **4** and **12**−**14** is that hydrazone **16** is unable to undergo C2-epimerization under the reaction conditions.

Scheme 5. Synthesis of Chiral 2,2-Disubstituted Oxetan-3-one 17[a]

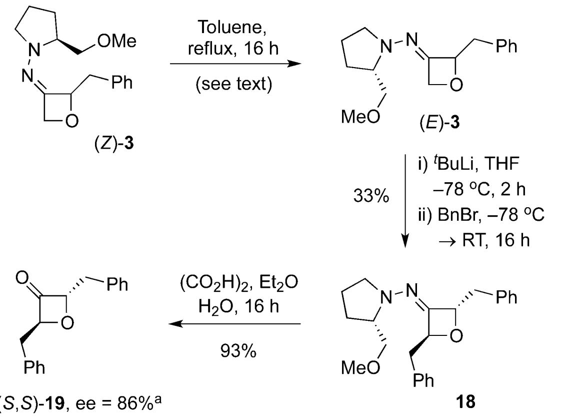


[a]ee determined by chiral GC analysis of acetates formed by $NaBH_4$ reduction of ketone **17**, followed by acetylation.

Alternatively, C_2-symmetric 2,4-dibenzyloxetan-3-one (*S*,*S*)-**19** was prepared in an excellent 86% ee, albeit in modest yield, by the benzylation of a 68:13:19 mixture of *E*(*S*):*E*(*R*):*Z*(*S*) hydrazone (*E*)-**3**, which was formed by heating a 88:12 mixture of *Z*(*S*):*Z*(*R*) hydrazone (*Z*)-**3** in refluxing in toluene for 16 h (Scheme 6) (see the Supporting Information).[19] Although the co-running byproduct, (2*S*)-2-(methoxymethyl)-*N*-[2,2-dibenzyl-oxetan-3-ylidine]-1-pyrrolidinamine, could not be separated from **18** by chromatography, ketone **19** could be isolated pure after the hydrolysis step.

In conclusion, we have developed a practical and efficient asymmetric synthesis of 2-substituted oxetan-3-ones in high enantiomeric excesses (up to 84% ee) via the alkylation of the lithiated SAMP hydrazone of oxetan-3-one. The methodology can be extended to the synthesis of a chiral 2,2-disubstituted oxetan-3-one in 90% ee by a one-pot double alkylation protocol, and a chiral C2 symmetric 2,4-disubstituted oxetan-3-one in 86% ee by controlled thermal isomerization of the hydrazone *E*/*Z* configuration. Thus, a diverse range of chiral 2-substituted oxetan-3-one derivatives can be accessed in a direct manner by simple variation of the electrophile and reaction conditions. These products are expected to be useful in the preparation of novel oxetane containing scaffolds in drug discovery programs. An illustrative example is provided by the preparation of oxetane containing tetrahydro-β-carbolines containing three stereogenic centers from (*S*)-**4** by further Pictet−Spengler cyclization.

Scheme 6. Synthesis of Chiral C_2-Symmetric 2,4-Disubstitued Oxetan-3-one 19[a]



[a]ee determined by chiral HPLC analysis of acetates formed by $NaBH_4$ reduction of ketone **19**, followed by acetylation.

■ EXPERIMENTAL SECTION

(2*S*)-2-(Methoxymethyl)-*N*-oxetan-3-ylidine-1-pyrrolidinamine ((*S*)-1). (*S*)-(−)-1-Amino-2-(methoxymethyl)pyrrolidine (537 μL, 4.0 mmol) was added dropwise to stirred oxetan-3-one (513 μL, 8.0 mmol). The mixture was heated to 55 °C for 16 h, and the excess oxetan-3-one and water were removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 85:14:1, hexane/ethyl acetate/triethylamine) to give (*S*)-**1** (735 mg, 100%) as a colorless oil: R_f (85:14:1, hexane/ethyl acetate/triethylamine) 0.16; ν_{max} (film)/cm^{-1} 2922, 2857, 1683, 1459, 1196, 1113, 956, 854; δ_H (400 MHz, $CDCl_3$) 5.47−5.41 (1H, m), 5.35−5.25 (3H, m), 3.50 (1H, dd, *J* = 9.2, 4.1 Hz), 3.40−3.33 (2H, m), 3.38 (3H, s), 3.20−3.13 (1H, m), 2.78 (1H, q, *J* = 8.2 Hz), 1.98−1.84 (3H, m), 1.78−1.68 (1H, m); δ_C (125 MHz, $CDCl_3$) 140.7 (C), 83.0 (CH_2), 82.5 (CH_2), 74.8 (CH_2), 65.0 (CH), 59.3 (CH_3), 52.6 (CH_2), 25.9 (CH_2), 22.7 (CH_2); *m*/*z* (ES^+) 185 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 185.1286, $C_9H_{16}N_2O_2$ requires $(MH)^+$, 185.1285; $[\alpha]_D^{25}$ −8.8 (*c* 0.12, $CHCl_3$).

(2*R*)-2-(Methoxymethyl)-*N*-oxetan-3-ylidine-1-pyrrolidinamine (1). Compound (*R*)-**1** was prepared by the method described for (*S*)-**1** using (*R*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine instead of (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine. All NMR data were identical to that of (*S*)-**1**: $[\alpha]_D^{25}$ +9.2 (*c* 0.12, $CHCl_3$).

Synthesis of 3 and 8−11: General Procedure. *tert*-Butyllithium (1.7 M solution in pentanes, 1.1 equiv) was added dropwise to a stirred solution of **1** (0.6 mmol) in anhydrous THF (2 mL) at −78 °C under nitrogen. After 2 h at −78 °C, the electrophile (1.2 equiv) was added by syringe, and the solution was allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with ether (30 mL) and washed with pH 7 buffer solution (3 mL) and brine (3 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 85:14:1, hexane/ethyl acetate/triethylamine) to give the 2-substituted SAMP hydrazone.

(2S)-2-(Methoxymethyl)-N-[2-(S)-benzyloxetan-3-ylidine]-1-pyrrolidinamine ((Z)-3): pale yellow oil (70 mg from 0.350 mmol (*S*)-**1**, 73%); R_f (85:14:1, hexane/ethyl acetate/triethylamine) 0.17; ν_{max} (film)/cm^{-1} 2920, 2860, 1686, 1603, 1453, 1113, 959, 699; δ_H (400 MHz, $CDCl_3$) major isomer, 7.33−7.20 (5H, m), 5.67−5.61 (1H, m),

4.97 (1H, dd, J = 11.4, 1.7 Hz), 4.68 (1H, dd, J = 11.4, 3.4 Hz), 3.56 (1H, dd, J = 8.5, 3.4 Hz), 3.44−3.02 (5 H, m), 3.42 (3H, s), 2.74 (1H, q, J = 8.3 Hz), 2.06−1.86 (3H, m), 1.76−1.66 (1H, m); δ_C (100 MHz, $CDCl_3$) 145.4 (C), 136.4 (C), 129.9 (CH), 128.2 (CH), 126.6 (CH), 93.3 (CH), 79.3 (CH_2), 75.7 (CH_2), 65.9 (CH), 59.3 (CH_3), 53.6 (CH_2), 39.0 (CH_2), 26.6 (CH_2), 23.1 (CH_2); m/z (ES^+) 275 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 275.1755, $C_{16}H_{22}N_2O_2$ requires $(MH)^+$, 275.1754.

*(2S)-2-(Methoxymethyl)-N-[2-(S)-(3-phenylallyl)oxetan-3-ylidine]-1-pyrrolidinamine (**8**):* pale yellow oil (101 mg from 0.586 mmol (S)-**1**, 57%); R_f (85:14:1, hexane/ethyl acetate/triethylamine) 0.23; ν_{max} (film)/cm^{-1} 2922, 2861, 1686, 1597, 1448, 1112, 956, 746, 693; δ_H (400 MHz, $CDCl_3$) major isomer 7.38−7.18 (5H, m), 6.53 (1H, d, J = 15.9 Hz), 6.30 (1H, dt, J = 15.9, 7.2 Hz), 5.56−5.51 (1H, m), 5.13 (2H, d, J = 2.5 Hz), 3.54 (1H, dd, J = 9.0, 3.9 Hz), 3.46−3.26 (3H, m), 3.37 (3H, s), 2.80−2.65 (3H, m), 2.05−1.95 (1H, m), 1.93−1.85 (2H, m), 1.73−1.63 (1H, m); δ_C (100 MHz, $CDCl_3$) 146.1 (C), 137.4 (C), 133.5 (CH), 128.5 (CH), 127.3 (CH), 126.2 (CH), 124.2 (CH), 92.7 (CH), 79.5 (CH_2), 75.8 (CH_2), 65.8 (CH), 59.3 (CH_3), 53.7 (CH_2), 36.6 (CH_2), 26.7 (CH_2), 23.0 (CH_2); m/z (ES^+) 301 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 301.1917, $C_{18}H_{24}N_2O_2$ requires $(MH)^+$, 301.1911.

*(2S)-2-(Methoxymethyl)-N-[2-(S)-octyloxetan-3-ylidine]-1-pyrrolidinamine (**9**):* pale yellow oil (105 mg from 0.586 mmol (S)-**1**, 60%), R_f (85:14:1, hexane/ethyl acetate/triethylamine) 0.29; ν_{max} (film)/cm^{-1} 2923, 2855, 1691, 1459, 1197, 1115, 957; δ_H (400 MHz, $CDCl_3$) major isomer 5.48−5.42 (1H, m), 5.12 (2H, d, J = 2.6 Hz), 3.54 (1H, dd, J = 8.9, 3.7 Hz), 3.40−3.18 (3H, m), 3.37 (3H, s), 2.68 (1H, q, J = 8.3 Hz), 2.05−1.60 (6H, m), 1.52−1.40 (2H, m), 1.39−1.20 (10H, m), 0.88 (3H, t, J = 6.6 Hz); δ_C (100 MHz, $CDCl_3$) 146.9 (C), 93.6 (CH), 79.2 (CH_2), 75.7 (CH_2), 65.7 (CH), 59.3 (CH_3), 53.5 (CH_2), 32.8 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 26.6 (CH_2), 24.4 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3); m/z (ES^+) 297 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 297.2535, $C_{17}H_{32}N_2O_2$ requires $(MH)^+$, 297.2537.

*(2S)-2-(Methoxymethyl)-N-[2-(S)-[3-(tert-butyldimethylsilanyl-oxy)propyl]oxetan-3-ylidene]-1-pyrrolidinamine (**10**):* pale yellow oil (142 mg from 0.586 mmol (S)-**1**, 68%); R_f (85:14:1, hexane/ethyl acetate/triethylamine) 0.19; ν_{max} (film)/cm^{-1} 2927, 2856, 1462, 1253, 1094, 958, 832, 774; δ_H (400 MHz, $CDCl_3$) major isomer 5.52−5.47 (1H, m), 5.12 (2H, d, J = 2.6 Hz), 3.66 (2H, t, J = 6.3 Hz), 3.54 (1H, dd, J = 9.1, 4.0 Hz), 3.38−3.21 (3H, m), 3.37 (3H, s), 2.67 (1H, q, J = 8.3 Hz), 2.20−1.60 (8H, m), 0.89 (9H, s), 0.05 (6H, s); δ_C (125 MHz, $CDCl_3$) 146.3 (C), 93.3 (CH), 79.2 (CH_2), 75.8 (CH_2), 65.7 (CH), 62.6 (CH_2), 59.3 (CH_3), 53.4 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 26.7 (CH_2), 25.9 (CH_3), 22.9 (CH_2), −5.27 (CH_3); m/z (ES^+) 357 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 357.2572, $C_{18}H_{36}N_2O_3Si$ requires $(MH)^+$, 357.2568.

*3-[[(2S)-2-(Methoxymethyl)-1-pyrrolidinyl]imino]-α-phenyloxetane-2-methanol (**11**).* Purified by flash column chromatography (SiO_2, 49:49:2, hexane/ethyl acetate/triethylamine); pale yellow oil (105 mg from 0.586 mmol (S)-**1**, 62%), mixture of isomers; R_f (49:49:2, hexane/ethyl acetate/triethylamine) 0.19; ν_{max} (film)/cm^{-1} 3395, 2863, 1724, 1603, 1452, 1195, 1096, 956, 700; δ_H (300 MHz, $CDCl_3$) see the Supporting Information; δ_C (125 MHz, $CDCl_3$) see the Supporting Information; m/z (ES^+) 291 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 291.1705, $C_{16}H_{22}N_2O_3$ requires $(MH)^+$, 291.1703.

*(2S)-2-(Methoxymethyl)-N-[2-(R)-allyl-2-benzyloxetan-3-ylidine]-1-pyrrolidinamine (**16**).* *tert*-Butyllithium (801 μL, 1.7 M solution in pentanes, 1.36 mmol, 1.1 equiv) was added dropwise to a stirred solution of (S)-**1** (228 mg, 1.24 mmol, 1 equiv) in anhydrous THF (5 mL) at −78 °C under nitrogen. After 2 h at −78 °C, benzyl bromide (162 μL, 1.36 mmol, 1.1 equiv) was added by syringe, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was recooled to −78 °C, and *tert*-butyllithium (801 μL, 1.7 M solution in pentanes, 1.36 mmol, 1.1 equiv) was added dropwise by syringe to give a dark brown solution. After 2 h at −78 °C, allyl bromide (118 μL, 1.36 mmol, 1.1 equiv) was added, and the reaction mixture was allowed to warm slowly to room temperature. The mixture was diluted with ether (30 mL) and washed with pH7 buffer solution (3 mL) and brine (3 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 85:14:1, hexane/ethyl acetate/triethylamine) to give **16** (128 mg, 33%) as a colorless oil: R_f (85:14:1, hexane/ethyl acetate/triethylamine) 0.42; ν_{max} (film)/cm^{-1} 2920, 2859, 1640, 1603, 1495, 1453, 1112, 959, 699; δ_H (400 MHz, $CDCl_3$) major isomer 7.40−7.16 (5H, m), 6.00−5.86 (1H, m), 5.17 (1H, d, J = 5.6 Hz), 5.15 (1H, d, J = 10.9 Hz), 4.70 (1H, d, J = 11.1 Hz), 4.46 (1H, d, J = 11.1 Hz), 3.48 (1H, dd, J = 9.0, 4.0 Hz), 3.42−2.92 (4H, m), 3.34 (3H, s), 3.20 (1H, d, J = 14.2 Hz), 3.02 (1H, d, J = 14.2 Hz), 2.64 (1H, dd, J = 14.7, 6.6 Hz), 2.41 (1H, dd, J = 14.6, 7.6 Hz), 2.10−1.60 (4H, m); δ_C (100 MHz, $CDCl_3$) 150.3 (C), 136.3 (C), 132.9 (CH), 130.5 (CH), 128.1 (CH), 126.7 (CH), 118.7 (CH_2), 101.4 (CH_2), 76.7 (CH_2), 75.3 (CH_2), 66.1 (CH), 59.2 (CH_3), 55.8 (CH_2), 43.9 (CH_2), 41.8 (CH_2), 26.6 (CH_2), 23.1 (CH_2); m/z (ES^+) 315 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 315.2068, $C_{19}H_{26}N_2O_2$ requires $(MH)^+$, 315.2067.

*(2S)-2-(Methoxymethyl)-N-[2,4-(S,S)-dibenzyloxetan-3-ylidine]-1-pyrrolidinamine (**18**).* (2S)-2-(Methoxymethyl)-N-[2-benzyloxetan-3-ylidine]-1-pyrrolidinamine (Z)-(**3**) (88% Z(S) and 12% Z(R) by ^{1}H NMR, see the Supporting Information) (450 mg, 1.64 mmol) was dissolved in anhydrous toluene (5 mL) and heated to reflux for 16 h. The solvent was removed under reduced pressure to give (E)-**3** (450 mg, 1.64 mmol) (19% Z(S), 68% E(S), and 13% E(R) by ^{1}H NMR), which was dissolved in anhydrous THF (10 mL) under nitrogen. The solution was cooled to −78 °C, and *tert*-butyllithium (1.06 mL, 1.7 M solution in pentanes, 1.81 mmol, 1.1 equiv) was added dropwise by syringe to give a dark brown solution. After 2 h at −78 °C, benzyl bromide (234 μL, 1.97 mmol, 1.2 equiv) was added by syringe, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with ether (30 mL) and washed with pH7 buffer solution (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 85:14:1, hexane/ethyl acetate/triethylamine) to give **18** (199 mg, 33%) as a pale yellow oil together with inseparable (2S)-2-(methoxymethyl)-N-[2,2-dibenzyl-oxetan-3-ylidine]-1-pyrrolidinamine (30 mg, 5%): R_f (85:14:1, hexane/ethyl acetate/triethylamine) 0.27; ν_{max} (film)/cm^{-1} 2913, 2874, 1686, 1603, 1496, 1453, 1113, 962, 697; δ_H (400 MHz, $CDCl_3$) major isomer 7.40−7.14 (10H, m), 5.20−5.14 (1H, m), 5.00−4.94 (1H, m), 3.54 (1H, dd, J = 8.9, 3.9 Hz), 3.45−3.30 (3H, m), 3.40 (3H, s), 3.15−2.90 (4H, m), 2.36 (1H, q, J = 8.2 Hz), 2.05−1.60 (4H, m); δ_C (100 MHz, $CDCl_3$) 148.0 (C), 136.9 (C), 136.7 (C), 130.3 (CH), 130.0 (CH), 128.1 (CH), 128.0 (CH), 126.6 (CH), 126.4 (CH), 90.7 (CH), 89.7 (CH), 75.7 (CH_2), 65.9 (CH), 59.3 (CH_3), 53.7 (CH_2), 40.8 (CH_2), 38.8 (CH_2), 26.7 (CH_2), 23.2 (CH_2); m/z (ES^+) 387 (MNa^+); HRMS (ESI-TOF) found $(MNa)^+$ 387.2046, $C_{23}H_{28}N_2O_2$ requires $(MNa)^+$, 387.2043.

Synthesis of 4, 12−15, 17, and 19: General Procedure. The 2-substituted SAMP hydrazone (0.24 mmol) was stirred vigorously in a mixture of saturated aqueous oxalic acid solution (2 mL) and diethyl ether (3 mL) at room temperature for 2−96 h (for the reaction time of each hydrazone see below). The reaction mixture was diluted with diethyl ether (20 mL), the layers were separated, and the organic layer was washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ketone was purified by flash column chromatography.

*(2S)-2-Benzyloxetan-3-one (**4**):* reaction time 2 h, purified by flash column chromatography (SiO_2, 2:1, hexane/diethyl ether); colorless oil (122 mg from 0.950 mmol **3**, 79%); R_f (2:1, hexane/diethyl ether) 0.50; ν_{max} (film)/cm^{-1} 2913, 1814, 1603, 1495, 1454, 1079, 955, 740, 698; δ_H (400 MHz, $CDCl_3$) 7.33−7.21 (5H, m), 5.65 (1H, td, J = 5.8, 4.6 Hz), 5.18 (1H, d, J = 15.0 Hz), 4.94 (1H, dd, J = 15.0, 4.6 Hz), 3.12 (2H, d, J = 5.8 Hz); δ_C (100 MHz, $CDCl_3$) 202.3 (CO), 135.3 (C), 129.6 (CH), 128.6 (CH), 127.0 (CH), 103.6 (CH), 89.0 (CH_2), 37.5 (CH_2); m/z (ES^+) 163 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 163.0758, $C_{10}H_{10}O_2$ requires $(MH)^+$, 163.0754; $[\alpha]_D^{26}$ −60 (c 0.07, $CHCl_3$); 74% ee (determined by chiral GC analysis of the acetates

formed by $NaBH_4$ reduction of **4**, then acetylation of the resulting mixture of alcohols; see the Supporting Information).

*(2S)-2-(3-Phenylallyl)oxetan-3-one (**12**):* reaction time 2 h, purified by flash column chromatography (SiO_2, 9:1, hexane/ethyl acetate); colorless oil (32 mg from 0.220 mmol **8**, 77%); R_f (9:1, hexane/ethyl acetate) 0.27; ν_{max} (film)/cm^{-1} 2912, 1815, 1595, 1493, 1069, 956, 741, 692; δ_H (400 MHz, $CDCl_3$) 7.38−7.20 (5H, m), 6.55 (1H, d, J = 15.9 Hz), 6.21 (1H, dt, J = 15.9, 7.2 Hz), 5.60−5.54 (1H, m), 5.30 (1H, d, J = 14.8 Hz), 5.22 (1H, dd, J = 14.8, 4.3 Hz), 2.78−2.72 (2H, m); δ_C (100 MHz, $CDCl_3$) 202.4 (CO), 136.9 (C), 134.3 (CH), 128.6 (CH), 127.6 (CH), 126.3 (CH), 122.2 (CH), 102.8 (CH), 89.2 (CH_2), 34.8 (CH_2); m/z (ES^+) 189 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 189.0910, $C_{12}H_{12}O_2$ requires $(MH)^+$, 189.0910; $[\alpha]_D^{26}$ −135 (c 0.13, $CHCl_3$); 84% ee (determined by chiral GC analysis of the acetates formed by $NaBH_4$ reduction of **12**, then acetylation of the resulting mixture of alcohols; see the Supporting Information).

*(2S)-2-Octyloxetan-3-one (**13**):* reaction time 2 h, purified by flash column chromatography (SiO_2, 9:1, hexane/ethyl acetate); colorless oil (38 mg from 0.243 mmol **9**, 85%); R_f (9:1, hexane/ethyl acetate) 0.58; ν_{max} (film)/cm^{-1} 2924, 2855, 1820, 1466, 1069, 961; δ_H (400 MHz, $CDCl_3$) 5.49−5.43 (1H, m), 5.28 (1H, dd, J = 15.0, 1.0 Hz), 5.21 (1H, dd, J = 15.0, 4.2 Hz), 1.87−1.80 (2H, m), 1.55−1.20 (12H, m), 0.88 (3H, t, J = 6.7 Hz); δ_C (100 MHz, $CDCl_3$) 203.6 (CO), 104.0 (CH), 88.7 (CH_2), 31.8 (CH_2), 31.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3); m/z (ES^+) 185 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 185.1539, $C_{11}H_{20}O_2$ requires $(MH)^+$, 185.1536; $[\alpha]_D^{25}$ −37 (c 0.17, $CHCl_3$) ; 83% ee (determined by chiral GC analysis of the acetates formed by $NaBH_4$ reduction of **13**, then acetylation of the resulting mixture of alcohols; see the Supporting Information).

*(6S)-2,7-Dioxabicyclo[4.2.0]octan-1-ol (**14**):* reaction time 4 h, purified by flash column chromatography (SiO_2, 1:1, hexane/ethyl acetate); colorless oil (25 mg from 0.323 mmol **10**, 60%), mixture of diastereoisomers, R_f (9:1, hexane/ethyl acetate) 0.27; ν_{max} (film)/cm^{-1} 3322, 2943, 1819, 1728, 1322, 1163, 1038, 927, 786; δ_H (300 MHz, $CDCl_3$) major diastereosiomer 4.77 (1H, d, J = 5.8 Hz), 4.47 (1H, d, J = 7.9 Hz), 4.23 (1H, dd, J = 7.9, 1.3 Hz), 3.86−3.77 (1H, m), 3.56 (1H, td, J = 11.3, 2.0 Hz), 3.50−2.80 (1H, br s), 2.05−1.40 (4H, m); δ_C (75 MHz, $CDCl_3$) 103.1 (CH), 93.9 (C), 88.2 (C), 82.4 (CH), 80.8 (CH_2), 61.3 (CH_2), 24.0 (CH_2), 18.9 (CH_2); m/z (ES^+) 131 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 131.0703, $C_6H_{10}O_3$ requires $(MH)^+$, 131.0703; $[\alpha]_D^{26}$+34 (c 0.166, $CHCl_3$) ; 84% ee (determined by chiral GC analysis of the monocyclic acetates formed from **14**; see the Supporting Information).

*(2S)-2-[(R)-Hydroxyphenylmethyl]oxetan-3-one (**15a**) and (2S)-2-[(S)-Hydroxyphenylmethyl]oxetan-3-one (**15b**).* Reaction time: 2 h. Purified by flash column chromatography (SiO_2, 1:1, hexane/ethyl acetate) to give a white crystalline solid (45 mg from 0.276 mmol **11**, 92%, 1.04:1.00 mixture of **15a**:**15b** by ^{1}H NMR, i.e., 47% **15a** and 45% **15b**, de = 4%), and then repurified by flash column chromatography (SiO_2, 1:1, hexane/ethyl acetate) to give **15a** as a white crystalline solid: mp 90−91 °C; R_f (1:1, hexane/ethyl acetate) 0.57; ν_{max} (film)/cm^{-1} 3401, 1821, 1494, 1086, 1068, 939, 888, 731, 694; δ_H (300 MHz, $CDCl_3$) 7.44−7.30 (5H, m), 5.61−5.57 (1H, m), 5.37−5.23 (2H, m), 5.08−5.02 (1H, br m), 2.72−2.52 (1H, br s); δ_C (150 MHz, $CDCl_3$) 199.8 (CO), 138.6 (C), 128.8 (CH), 128.6 (CH), 126.5 (CH), 106.1 (CH), 90.5 (CH_2), 72.4 (CH); m/z (ES^+) 201 (MNa^+); HRMS (ESI-TOF) found $(MNa)^+$ 201.0525, $C_{10}H_{10}O_3$ requires $(MH)^+$, 201.0522; $[\alpha]_D^{26}$−120 (c 0.086, $CHCl_3$); 54% ee (determined by chiral GC; see the Supporting Information) and **15b** as a white crystalline solid: mp 109−110 °C; R_f (1:1, hexane/ethyl acetate) 0.48; ν_{max} (film)/cm^{-1} 3398, 1819, 1492, 1413, 1062, 944, 751, 699; δ_H (300 MHz, $CDCl_3$) 7.44−7.30 (5H, m), 5.59−5.55 (1H, m), 5.33−5.20 (2H, m), 5.08 (1H, d, J = 3.4 Hz), 2.80−2.68 (1H, br s); δ_C (150 MHz, $CDCl_3$) 199.3 (CO), 137.1 (C), 128.8 (CH), 128.7, (CH), 126.8 (CH), 106.3 (CH), 90.4 (CH_2), 73.7 (CH); m/z (ES^+) 201 (MNa^+); HRMS (ESI-TOF) found $(MNa)^+$ 201.0525, $C_{10}H_{10}O_3$ requires $(MH)^+$, 201.0522; $[\alpha]_D^{26}$ +8 (c 0.084, $CHCl_3$); 2% ee (determined by chiral GC; see the Supporting Information).

*(2R)-2-Allyl-2-benzyloxetan-3-one (**17**):* reaction time 4 days, purified by flash column chromatography (SiO_2, 19:1, hexane/ethyl acetate); colorless oil (31 mg from 0.296 mmol **16**, 52%); R_f (19:1, hexane/ethyl acetate) 0.33; ν_{max} (film)/cm^{-1} 2909, 1814, 1640, 1496, 1427, 955, 700; δ_H (400 MHz, $CDCl_3$) 7.33−7.22 (5H, m), 5.97−5.85 (1H, m), 5.21 (1H, d, J = 10.5 Hz), 5.19 (1H, d, J = 6.0 Hz), 4.89 (1H, d, J = 14.9 Hz), 4.47 (1H, d, J = 14.9 Hz), 3.06 (1H, d, J = 14.3 Hz), 2.98 (1H, d, J = 14.3 Hz), 2.54 (2H, d, J = 7.4 Hz); δ_C (125 MHz, $CDCl_3$) 205.1 (CO), 135.1 (C), 131.0 (CH), 130.5 (CH), 128.4 (CH), 127.0 (CH), 120.1 (CH_2), 111.4 (C), 86.7 (CH_2), 41.3 (CH_2), 39.8 (CH_2); m/z (ES^+) 225 (MNa^+); HRMS (ESI-TOF) found $(MNa)^+$ 225.0889, $C_{13}H_{14}O_2$ requires $(MNa)^+$, 225.0886; $[\alpha]_D^{25}$ +43 (c 0.34, $CHCl_3$); 90% ee (determined by chiral GC analysis of the acetates formed by $NaBH_4$ reduction of **17**, then acetylation of the resulting mixture of alcohols; see the Supporting Information).

*(2S,4S)-2,4-Dibenzyloxetan-3-one (**19**):* reaction time 16 h, purified by flash column chromatography (SiO_2, 19:1, hexane/ethyl acetate); colorless oil (112 mg from 0.477 mmol **18**, 93%); R_f (19:1, hexane/ethyl acetate) 0.27; ν_{max} (film)/cm^{-1} 3029, 2912, 1813, 1603, 1496, 1454, 954, 696; δ_H (400 MHz, $CDCl_3$) 7.29−7.18 (10H, m), 5.23−5.18 (2H, m), 3.08−2.98 (4H, m); δ_C (100 MHz, $CDCl_3$) 204.4 (CO), 135.5 (C), 129.7 (CH), 128.6 (CH), 127.2 (CH), 100.4 (CH), 37.4 (CH_2); m/z (ES^+) 275 (MNa^+); HRMS (ESI-TOF) found $(MNa)^+$ 275.1048, $C_{17}H_{16}O_2$ requires $(MNa)^+$, 275.1043; $[\alpha]_D^{25}$ −90 (c 0.58, $CHCl_3$); 86% ee (determined by chiral HPLC analysis of the acetates formed by $NaBH_4$ reduction of **19**, then acetylation of the resulting mixture of alcohols; see the Supporting Information).

*(2S,3S,3′S)-Ethyl-2-benzyl-2′,3′,4′,9′-tetrahydrospiro[oxetane-3,1′-pyrido[3,4-b]indole]-3′-carboxylate (**6**) and (2R,3R,3′S)-Ethyl-2-benzyl-2′,3′,4′,9′-tetrahydrospiro[oxetane-3,1′-pyrido[3,4-b]-indole]-3′-carboxylate (**7**).* 2-Benzyloxetan-3-one (**4**) (57 mg, 0.35 mmol), (S)-ethyl 2-amino-3-(1H-indol-3-yl)propanoate (98 mg, 0.42 mmol, 1.2 equiv), and iodine (4.5 mg, 0.0176 mmol, 0.05 equiv) in anhydrous acetonitrile (2.5 mL) were heated to reflux under nitrogen for 18 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (10 mL) and washed with saturated $Na_2S_2O_3$ solution (10 mL), saturated $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give the title compounds as a 7.4:1 mixture of diastereoisomers as determined by ^{1}H NMR spectroscopy. Purification by flash column chromatography (SiO_2, 20:80:1, ethyl acetate/petroleum ether/triethylamine) gave less polar, major diastereoisomer **6** (89 mg, 67%) as an off-white solid: mp 60−65 °C; ν_{max} (film)/cm^{-1} 3263, 2937, 1731, 1494, 1453, 1369, 1182, 967, 742, 701; δ_H (400 MHz, $CDCl_3$) 8.98 (1H, s), 7.54 (1H, d, J = 7.8 Hz), 7.41 (1H, d, J = 7.9 Hz), 7.30−7.14 (7H, m), 5.18 (1H, dd, J = 9.4, 3.6 Hz), 4.85 (1H, d, J = 6.2 Hz), 4.81 (1H, d, J = 6.2 Hz), 4.34 (2H, q, J = 7.1 Hz), 3.77 (1H, dd, J = 10.5, 4.1 Hz), 3.39 (1H, dd, J = 14.1, 9.5 Hz), 3.26−3.13 (2H, m), 2.87 (1H, dd, J = 15.1, 10.5 Hz), 2.90−2.70 (1H, br s), 1.40 (3H, t, J = 7.1, CH_3); δ_C (100 MHz, $CDCl_3$) 172.9 (C═O), 137.1 (C), 136.4 (C), 133.9 (C), 129.3 (CH), 128.6 (CH), 126.6 (CH), 126.6 (C) 122.4 (CH), 119.8 (CH), 118.3 (CH), 111.3 (CH), 108.5 (C), 91.7 (CH), 83.1 (CH_2), 61.4 (CH_2), 58.3 (C), 53.8 (CH), 36.8 (CH_2), 25.5 (CH_2), 14.2 (CH_3); m/z (ES^+) 377 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 377.1863, $C_{23}H_{24}N_2O_3$ requires $(MH)^+$, 377.1860; $[\alpha]_D^{23}$ −65 (c 0.16, $CHCl_3$), and more polar, minor diastereoisomer **7** (12 mg, 9%) as an off-white solid: ν_{max} (film)/cm^{-1} 3307, 2926, 1730, 1495, 1453, 1370, 1182, 977, 744, 701; (400 MHz, $CDCl_3$) 8.68 (1H, s), 7.53 (1H, d, J = 7.8 Hz), 7.43 (1H, d, J = 8.0 Hz), 7.33−7.14 (7H, m), 5.06 (1H, dd, J = 8.0, 5.9 Hz), 4.93 (1H, d, J = 6.8 Hz), 4.86 (1H, d, J = 6.8 Hz), 4.29 (2H, q, J = 7.1 Hz), 3.46−3.34 (2H, m), 3.20 (1H, dd, J = 14.1, 5.8 Hz), 3.09 (1H, dd, J = 15.1, 4.4 Hz), 2.86 (1H, dd, J = 15.1, 9.6 Hz), 1.8−1.2 (1H, br s), 1.38 (3H, t, J = 7.1 Hz); δ_C (100 MHz, $CDCl_3$) 173.1 (C═O), 136.7 (C), 136.3 (C), 134.7 (C), 129.2 (CH), 128.6 (CH), 126.6 (CH), 126.5 (C), 122.4 (CH), 119.8 (CH), 118.3 (CH), 111.2 (CH), 108.3 (C), 93.5 (CH), 81.2 (CH_2), 61.3 (CH_2), 57.9 (C), 54.1 (CH), 36.9 (CH_2), 25.2 (CH_2), 14.3 (CH_3); m/z (ES^+) 377 (MH^+); HRMS (ESI-TOF)

dx.doi.org/10.1021/jo4020485 | J. Org. Chem. 2013, 78, 12243−12250

found $(MH)^+$ 377.1865, $C_{23}H_{24}N_2O_3$ requires $(MH)^+$, 377.1860; $[\alpha]_D^{23}$ +13 (*c* 0.08, $CHCl_3$).

N,N-Dimethyl-N′-oxetan-3-ylidenehydrazine (**5**). *N,N*-Dimethylhydrazine (888 μL, 11.7 mmol) was added dropwise to stirred oxetan-3-one (898 μL, 14.0 mmol). The mixture was heated to 65 °C for 16 h, and the excess 3-oxetanone and water were removed under reduced pressure to give **5** (1.26 g, 94%) as a pale yellow oil which was used without further purification: R_f (1:1, petroleum ether/ethyl acetate) 0.29; ν_{max} (film)/cm^{-1} 3363, 2952, 2861, 1820, 1685, 1467, 1446, 1240, 1144, 1024, 960, 857; δ_H (400 MHz, $CDCl_3$) 5.42 (2H, t, *J* = 2.9 Hz), 5.29 (2H, t, *J* = 2.9 Hz), 2.68 (6H, s); δ_C (100 MHz, $CDCl_3$) 142.4 (C), 82.2 (CH_2), 81.3 (CH_2), 45.7 (CH_3); *m/z* (ES^+) 115 (MH^+); HRMS (ESI-TOF) found $(MH)^+$ 115.0870, $C_5H_{10}N_2O$ requires $(MH)^+$, 115.0866.

General Procedure for the Preparation of Racemic 2-Substituted Oxetan-3-ones 4, and 12−15. *tert*-Butyllithium (1.7 M solution in pentanes, 1.1 equiv) was added dropwise to a stirred solution of **5** (1.37 mmol) in anhydrous THF (5.5 mL) at −78 °C under nitrogen. After 2 h at −78 °C, the electrophile (1.2 equiv) was added by syringe, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with ether (30 mL) and washed with pH 7 buffer solution (3 mL) and brine (3 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in a mixture of saturated aqueous oxalic acid solution (5 mL) and diethyl ether (20 mL) and stirred vigorously at room temperature for 2 h. The reaction mixture was diluted with diethyl ether (20 mL), the layers were separated, and the organic layer was washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ketone was purified by flash column chromatography as described above.

General Procedure for the Preparation of Acetates from Ketones 4, 12, 13, 17, and 19 for Chiral GC/HPLC Analysis. Sodium borohydride (1.5 equiv) was added to a stirred solution of the ketone (0.05 mmol) in anhydrous methanol (1 mL) at 0 °C. After 1 h, the reaction mixture was partitioned between dichloromethane (20 mL) and brine (5 mL). The layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give pure diastereoisomeric alcohols, as confirmed by ^{1}H NMR (see the Supporting Information).

4-(Dimethylamino)pyridine (1 crystal) and acetic anhydride (3 equiv) were added to a stirred solution of the alcohol in anhydrous dichloromethane (1 mL). After 3 h at room temperature, the reaction mixture was filtered through a small plug of silica which was washed well with ethyl acetate. The filtrate was concentrated in vacuo to give pure acetate derivatives as confirmed by ^{1}H NMR (see the Supporting Information).

Procedure for the Preparation of Acetates from Alcohol 14 for GC Analysis. 4-(Dimethylamino)pyridine (1 crystal) and acetic anhydride (22 μL, 0.264 mmol, 3 equiv) were added to a stirred solution of 2,7-dioxabicyclo[4.2.0]octan-1-ol (**14**) in anhydrous dichloromethane (1 mL). After 3 h at room temperature, the reaction mixture was filtered through a small plug of silica which was washed well with ethyl acetate. The filtrate was concentrated in vacuo to give pure monocyclic acetate derivatives (13 mg, 89%) as confirmed by ^{1}H NMR (see the Supporting Information).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of compounds **1** and **3−19**, X-ray crystal structures and data of compounds **6**, **7**, **15a**, and **15b** (CIF), copies of ^{1}H NMR spectra of alcohols and acetates prepared from **4**, **12−14**, **17**, and **19** for ee determination, copies of chiral GC and HPLC chromatograms of acetates and alcohols prepared from **4**, **12−14**, **17**, and **19** and alcohols **15a** and **15b**, and copies of ^{1}H NMR spectra of **3** before and after thermal isomerization. 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.

■ ACKNOWLEDGMENTS

We thank the EPSRC and the University of Warwick for financial support. We are grateful to Professor Martin Wills for providing access to chiral GC and HPLC instruments and to Dr. Rina Soni for her advice on GC and HPLC analysis. The Oxford Diffraction Gemini XRD system for X-ray structure determination was obtained through the Science City Advanced Materials project: Creating and Characterizing Next Generation Advanced Materials, with support from Advantage West Midlands.

■ REFERENCES

(1) For reviews see: (a) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227. (b) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052. (c) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Märki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4512. (d) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736.

(2) For recent papers, see: (a) Burkhard, J. A.; Wuitschik, G.; Plancher, J.-M.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2013**, *15*, 4312. (b) Fujishima, T.; Nozaki, T.; Suenga, T. *Bioorg. Med. Chem.* **2013**, *21*, 5209. (c) Nassoy, A.-C.; Raubo, P.; Harrity, J. P. A. *Tetrahedron Lett.* **2013**, *54*, 3094. (d) Beasley, B. O.; Clarkson, G. J.; Shipman, M. *Tetrahedron Lett.* **2012**, *53*, 2951. (e) Stepan, A. F.; Karki, K.; McDonald, W. S.; Dorff, P. H.; Dutra, J. K.; DiRico, K. J.; Won, A.; Subramanyam, C.; Efremov, I. V.; O'Donnell, C. J.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Sneed, B.; Sun, H.; Lu, Y.; Robshaw, A. E.; Riddell, D.; O'Sullivan, T. J.; Sibley, E.; Capetta, S.; Atchison, K.; Hallgren, A. J.; Miller, E.; Wood, A.; Obach, R. S. *J. Med. Chem.* **2011**, *54*, 7772. (f) Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944.

(3) Exceptions include biologically active oxetanes derived from natural products, e.g., paclitaxel; see ref 1b.

(4) For methods of oxetane synthesis, see: (a) Sharma, R.; Williams, L. J. *Org. Lett.* **2013**, *15*, 2202. (b) Park, H. J.; Yoon, U. C.; Lee, H.-Y.; Cho, D. W.; Cho, D. W.; Mariano, P. S. *J. Org. Chem.* **2012**, *77*, 10304. (c) Meagawa, T.; Otake, K.; Hirosawa, K.; Goto, A.; Fujioka, H. *Org. Lett.* **2012**, *14*, 4798. (d) Vigo, D.; Stasi, L.; Gagliardi, S. *Tetrahedron Lett.* **2011**, *52*, 565. (e) Kazakova, O. B.; Khusnutdinova, E. F.; Lobov, A. N.; Zvereva, T. I.; Suponitskii, K. Y. *Chem. Nat. Compd.* **2011**, *46*, 897. (f) Ghosh, P.; Zhang, Y.; Emge, T. J.; Williams, L. J. *Org. Lett.* **2009**, *11*, 4402. (g) Wuitschik, G.; Carreira, E. M.; Rogers-Evans, M.; Müller, K. *Process Chemistry in the Pharmaceutical Industry*; CRC Press: Boca Raton, 2008; Chapter 13, pp 217−229. (h) Dejeagher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29.

(5) For asymmetric synthesis of oxetanes, see: (a) Zhao, Q.-Y.; Huang, L.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2012**, *354*, 1926. (b) Mikami, K.; Aikawa, K.; Aida, J. *Synlett* **2011**, 2719. (c) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550. (d) Sone, T.; Gang, Lu.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1677. (e) Christlieb, M.; Davies, J. E.; Eames, J.; Hooley, R.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2983. (f) Soai, K.; Niwa, S.; Yamanoi, T.; Hikima, H.; Ishizaki, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1018.

(6) (a) For a review on *N,N*-dialkylhydrazones in organic synthesis, see: Lazny, R.; Nodzewska, A. *Chem. Rev.* **2010**, *110*, 1386. (b) For a

review on SAMP/RAMP-hydrazones, see: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.

(7) Our own attempts to form the enolate of oxetan-3-one with ^{t}BuLi at −78 °C, with subsequent trapping with BnBr, gave the product of direct addition to the ketone.

(8) Hazelard, D.; Fadel, A. *Tetrahedron: Asymmetry* **2005**, *16*, 2067.

(9) The ^{1}H NMR of **3** after purification by chromatography indicated a 88:12 mixture of stereoisomers deduced to be $Z(S)$:$Z(R)$; de = 76%. The de of hydrazones **8–11**, **16**, and **18** could not be determined accurately by NMR methods.

(10) Enders, D.; Wortmann, L.; Peters, R. *Acc. Chem. Res.* **2000**, *33*, 157.

(11) Enders, D.; Hundertmark, T.; Lazny, R. *Synlett* **1998**, 721.

(12) The ee of **4** (74%), determined by chiral GC analysis of its acetate derivatives, is comparable with the de of **3** (76%), determined by ^{1}H NMR.

(13) The overall yield of racemic ketone **4** prepared by the two-step alkylation/hydrolysis sequence from achiral hydrazone **5** was found to be low (19%). We speculate that the methoxy group of SAMP hydrazone **1** aids metalation via a complex-induced proximity effect (CIPE).

(14) Full details of the scope of this reaction will be disclosed separately. Beasley, B. O.; Alli-Balogun, A.; Clarkson, G. J.; Shipman, M. Manuscript in preparation.

(15) Koch, R. *Org. Biomol. Chem.* **2011**, *9*, 2885.

(16) If the assumption is made that the major enantiomer of both **15a** and **15b** has the (S) configuration at the C2 stereocenter, the de and ee values obtained by ^{1}H NMR and GC, respectively, indicate that the ratio of ($2S,\alpha R$):($2R,\alpha S$):($2S,\alpha S$):($2R,\alpha R$) isomers is 39.3:11.7:25.0:24.0. From this, the *Si* facial selectivity of the proposed azaenolate and the *Re* facial selectivity of the aldehyde may be calculated as 29% and 27%, respectively.

(17) (a) Smith, A. B., III; Ishiyama, H.; Cho, Y. S.; Ohmoto, K. *Org. Lett.* **2001**, *3*, 3967. (b) Enders, D.; Whitehouse, D. L.; Runsink, J. *Chem.—Eur. J.* **1995**, *1*, 382.

(18) (a) Enders, D.; Breuer, I.; Raabe, G. *Synthesis* **2005**, 3517. (b) Enders, D.; Nühring, A.; Runsink, J.; Raabe, G. *Synthesis* **2001**, 1406. (c) Mino, T.; Takagi, K.; Yamashita, M. *Synlett* **1996**, 645. (d) Enders, D.; Zamponi, A.; Schäfer, T.; Nübling, C.; Eichenauer, H.; Demir, A. S.; Raabe, G. *Chem. Ber.* **1995**, *127*, 1707. (e) Enders, D.; Zamponi, A.; Raabe, G. *Synlett* **1992**, 897.

(19) When **3** was heated to 50 °C for 23 h, isomerization from Z to E, as deduced by ^{1}H NMR, was found to be less than 50% complete. When **3** was heated to 110 °C for 16 h, when equilibrium had been achieved, **3** was found to exist as a 19:68:13 mixture of $Z(S)$:$E(S)$:$E(R)$ isomers. In contrast, Enders found that the alkylated SAMP hydrazones of 2,2-dimethyl-1,3-dioxan-5-one undergo rapid isomerization from Z to E on heating, with isomerization being complete after 15 min at 50 °C. See: Enders, D.; Bockstiegel, B. *Synthesis* **1989**, 493.