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Chemo-, Regio-, and Stereoselective Synthesis of Polysusbtituted Oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)ones via a Domino oxa-Michael/aza-Michael/Williamson Cycloetherification Sequence

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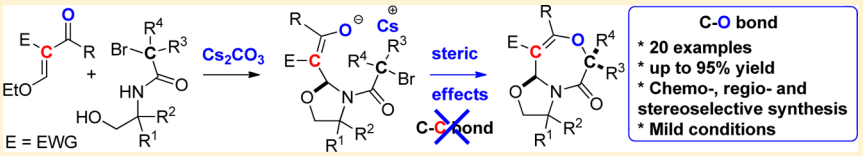
Supporting Information



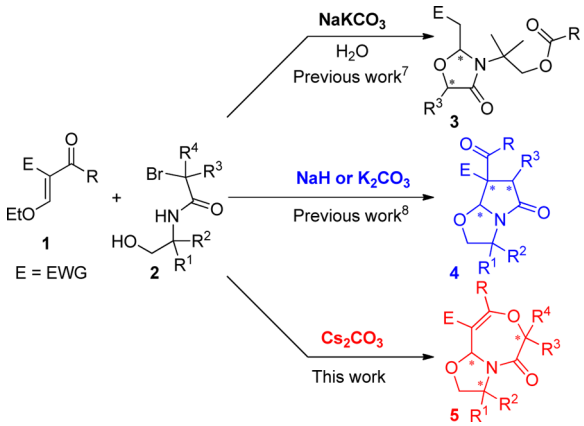
ABSTRACT: The access to new oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-ones starting from α-bromoamido alcohols and Michael acceptors under mild conditions is presented. This domino process proved to be chemo-, regio-, and stereoselective and allows the formation of a large diversity of highly functional 7-membered rings in good yields up to 95%. The complete shift of the regioselectivity of the intermediate enolate from a C−C to a C−O bond formation, contrary to the already known alkylations of such ambident nucleophiles, is mostly triggered by steric effects. The last step of the sequence was modeled by DFT giving some important insights for this C−C vs C−O bond shift.

INTRODUCTION

Structural diversity remains one of the greatest goals and challenges for both organic and pharmaceutical chemists.[1] This structural diversity, in order to be of maximum biological interest, has to lead to architecturally elaborate and if possible chiral frameworks. In this field, many efforts have been devoted to the development of powerful tools, such as combinatorial chemistry,[2] domino,[3] and/or multicomponent[4] reactions (MCR) and diversity-oriented synthesis (DOS).[5]

One way to access structural diversity proceeds via the alteration of the course/sequence of a domino process starting from the same substrates.[6] Indeed, by simple tuning of the reaction conditions, we were able to access three different skeletons (Scheme 1). In the presence of water and using $KNaCO_3$ as a base, Michael acceptors **1** and hydroxyl α-bromoamides **2** led to the formation of oxazolidin-4-ones **3**,[7] while in water free conditions and in the presence of NaH or K_2CO_3, the same substrates led efficiently to precursors of polysubstituted oxazolo-pyrrolidinones **4**.[8] We anticipated that the formation of 1,4-oxazepines **5** could be triggered during the last step of the latter domino process by shifting from a C−C to a C−O bond formation. In the present work, this new switch in the domino process provided access to 1,4-oxazepines **5**. Compared to the already known strategies for *O*- vs *C*-alkylation of enolates, where the reactivity of these ambident nucleophiles is usually dependent on the reaction conditions, such as the solvent, the cation, or the electrophile, in our case, the reactivity shift is mostly directed by steric effects.[9]

Scheme 1. Access to Oxazolidin-4-ones 3, Polysubstituted Bicyclic Lactams 4 and Oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-ones 5 Starting from the Same Substrates 1 and 2



Besides the interest of this selective change in the alkylation process of an intermediate enolate, the 1,4-oxazepine backbone is an important heterocyclic system found in several biologically relevant compounds.[10] Although many methods have been developed,[6a,11] interestingly the access to nonaromatic-fused systems remains scarce.[12]

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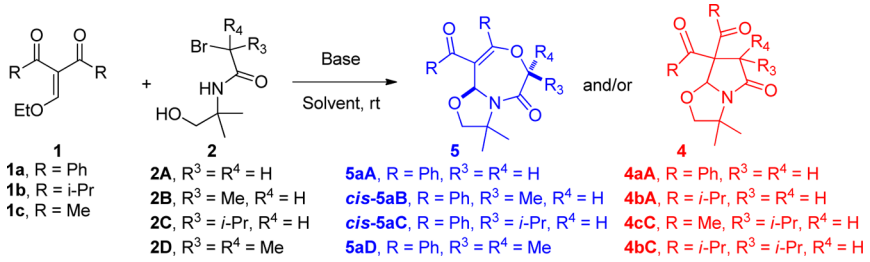
Table 1. Chemoselective Synthesis of Polysubstituted 1,4-Oxazepines 5[a]



1
1a, R = Ph
1b, R = i-Pr
1c, R = Me

2
2A, $R^3 = R^4 = H$
2B, R^3 = Me, R^4 = H
2C, R^3 = *i*-Pr, R^4 = H
2D, $R^3 = R^4$ = Me

5
5aA, R = Ph, $R^3 = R^4 = H$
***cis*-5aB**, R = Ph, R^3 = Me, R^4 = H
***cis*-5aC**, R = Ph, R^3 = *i*-Pr, R^4 = H
5aD, R = Ph, $R^3 = R^4$ = Me

4
4aA, R = Ph, $R^3 = R^4 = H$
4bA, R = *i*-Pr, $R^3 = R^4 = H$
4cC, R = Me, R^3 = *i*-Pr, $R^4 = H$
4bC, R = *i*-Pr, R^3 = *i*-Pr, $R^4 = H$

entry	solvent	base	product **5** or **4**	yield, %[b]	ratio **5**:**4**[c]
1	THF	NaH	**4aA**	64[d]	<2:98
2	THF	Cs_2CO_3	**4aA**		20:80
3	DMF	Cs_2CO_3	**4aA**		30:70
4	CH_3CN	Cs_2CO_3	**5aA**	30	55:45
5	CH_3CN	Cs_2CO_3	***cis*-5aB**	86	>98:2
6	CH_3CN	Cs_2CO_3	***cis*-5aC**	85	>98:2
7	THF	NaH	***cis*-5aC**	78	>98:2
8	CH_3CN[e]	Cs_2CO_3	**5aD**	51	>98:2
9	CH_3CN	Cs_2CO_3	**4bA**	60	<2:98[f]
10	CH_3CN	Cs_2CO_3	**4cC**	75	<2:98[f]
11	CH_3CN	Cs_2CO_3	**4bC**	48	<2:98[f]

[a]Typical conditions: Michael acceptor **1** (0.25 mmol, 1eq), α-bromoacetamide **2** (0.3 mmol, 1.2eq), and Cs_2CO_3 (0.25 mmol, 1 equiv) in 2 mL of acetonitrile were stirred for 12 h. [b]Isolated yields of the major product. [c]The ratios were determined from ^{1}H NMR of the crude mixture. [d]See ref 8a. [e]The reaction was run at 50 °C. [f]The presence of 1,4-oxazepines could not be clearly confirmed due to complication of ^{1}H NMR spectra of the crude mixture, thus the ratios were determined on the purified compound.

RESULTS AND DISCUSSION

At the outset, the reaction conditions were first tested starting from Michael acceptors **1a** (R = Ph) and hydroxyl α-bromoamide **2A** ($R^3 = R^4$ = H) as model substrates (Table 1, entries 1−4). From previously reported results,[8b] the use of NaH as the base in THF proved to chemoselectively lead to oxazolo-pyrrolidinone **4aA** in 64% yield (Table 1, entry 1). In order to promote *O*- vs *C*-alkylation of the intermediate enolate formed during the domino process, the use of Cs_2CO_3 was investigated.[6a] In the same solvent, the formation of the desired 7-membered ring **5aA** was observed but as the minor product (Table 1, entry 2). In order to overcome this poor selectivity, other solvents were screened. The best results were obtained when CH_3CN was employed, allowing the formation of 1,4-oxazepine **5aA** as the major product (Table 1, entry 4).

Gratifyingly, when α-bromo-α-methylacetamide **2B** was employed, the targeted product *cis*-**5aB** was isolated in good yield (86%) as the sole regio- and *cis*-diastereomer[13] (Table 1, entry 5). In the same conditions, the more sterically hindered isopropyl derivative **2C** was also efficiently converted in a good 85% yield (Table 1, entry 6). Interestingly, the same selectivity and almost the same yield were attained when employing NaH in THF, proving that in this case the selective enolate *O*-alkylation is mainly controlled by steric effects prior to the nature of the solvent, the cation or the leaving group (Table 1, entry 7). It was possible to synthesize, albeit with lower yield (51%), 1,4-oxazepine **5aD** bearing a *gem*-dimethyl moiety (Table 1, entry 8). Unfortunately, when starting from dialkylketone derived Michael acceptors **1b** (R = *i*-Pr) or **1c** (R = Me), no 1,4-oxazepine could be isolated (Table 1, entries 9−11). The structures of *cis*-**5aB** and **5aD** were confirmed by single crystal X-ray (Figure 1).

We then turned our attention to unsymmetrical diketone derived Michael acceptors (Scheme 2). In all the cases, a mixture of both regioisomers was obtained in yields ranging from 55% to 90% and with complete diastereoselectivity. The lack of regioselectivity in these cases is evidently due to the weak influence of electronic effects and to the poor steric discrimination between the aromatic substituents involved in the reaction.

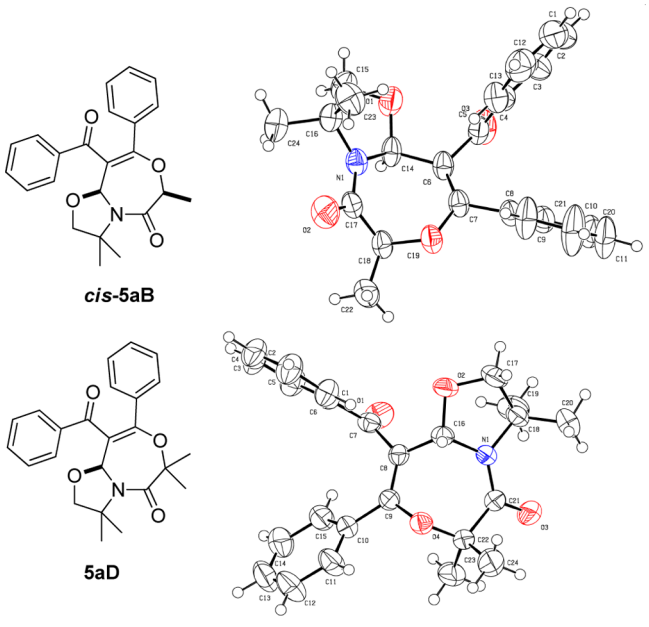


Figure 1. ORTEP of compounds *cis*-**5aB** and **5aD**.

As previously assessed,[8b] the domino sequence is under the kinetic control of the last step, the sequence leading to the intermediate **Int** being completely reversible (Scheme 3). For this last step, two competitive pathways leading to *C*-alkylation (path A) or to *O*-alkylation (path B) may be involved

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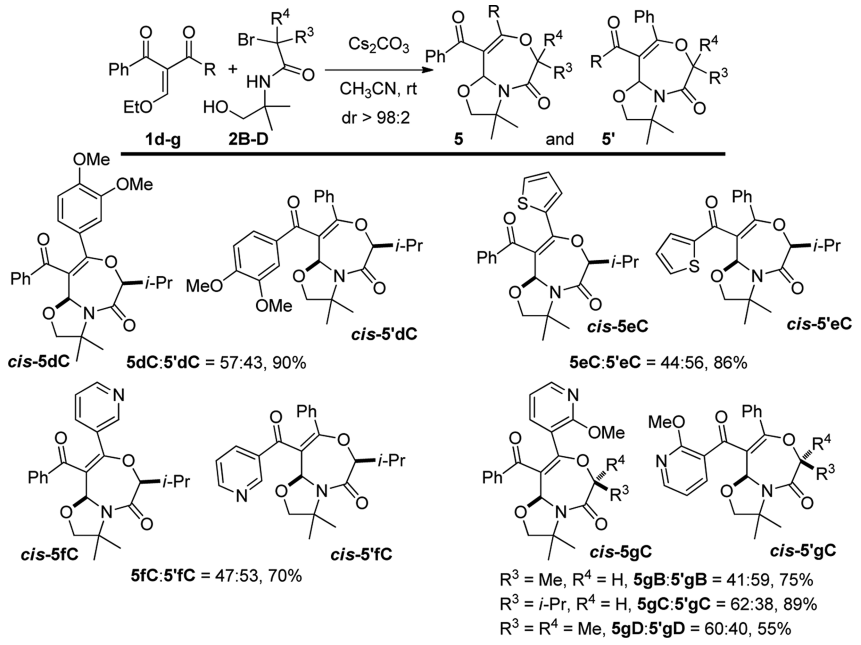
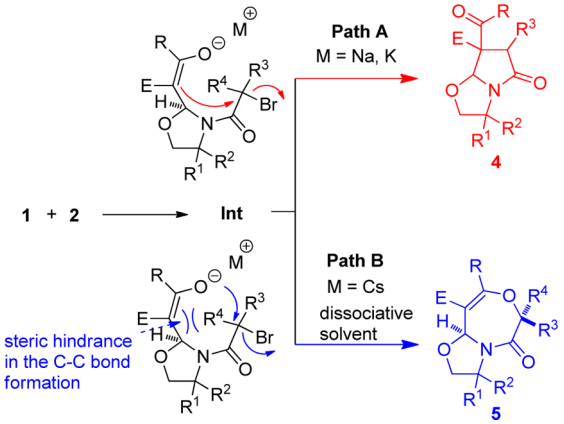
Scheme 2. Substrate Scope Starting from Unsymmetrical Diketones



Scheme 3. Proposed Mechanisms for the Divergent Synthesis of 4 and 5



depending on the substrate and the reaction conditions (soft counterion, polar solvent and bulkiness of the substituents).

In order to rationalize the process and improve our understanding of the factors influencing the *C*- vs *O*-alkylation, the last step of the sequence was modeled by DFT at the M06-2X/6-311+G(d,p) level[14] using the Gaussian 09 suite of programs.[15] M06-2X was described to provide reasonable energetics in the case of systems involving dispersion interactions[16] and in the calculation of transition states involving enolates.[17] Solvent effects were included using the SMD model for the description of acetonitrile as the solvent. Considering the highly dissociative activity of the solvent used and the very soft counterion involved (Cs^+), the effect of the cation on the energy profile was considered negligible and it was decided to perform the calculations on the free enolate to reduce the computation cost. The reaction was first modeled on **4aA** and **5aA**. Interestingly, although clearly less stable than **4aA** by 70 kJ/mol (Figure 2), the product **5aA** resulting from the *O*-alkylation was obtained in mixture with **4aA** in the reaction conditions (Table 1, entry 4). This is evidently the

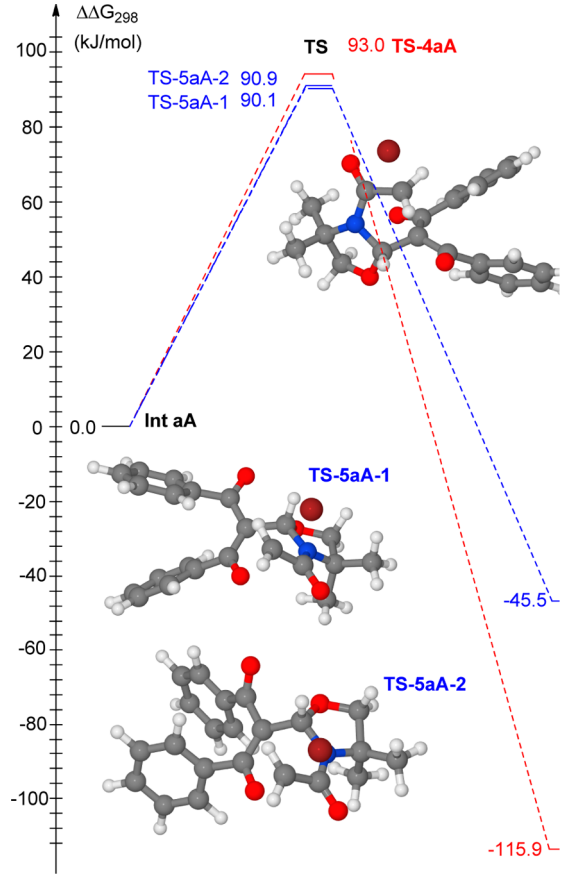


Figure 2. Last step of the reaction path to **4aA** and **5aA**. Gibbs free energies at 298 K in kJ/mol.

result of the poor control by the last transition state of the sequence related to the low energy gap existing between the transition states of each pathway (only 2.9 kJ/mol at rt) to be placed in relationship with the 55:45 ratio observed experimentally in favor of **5aA**. Because of the conjugation of

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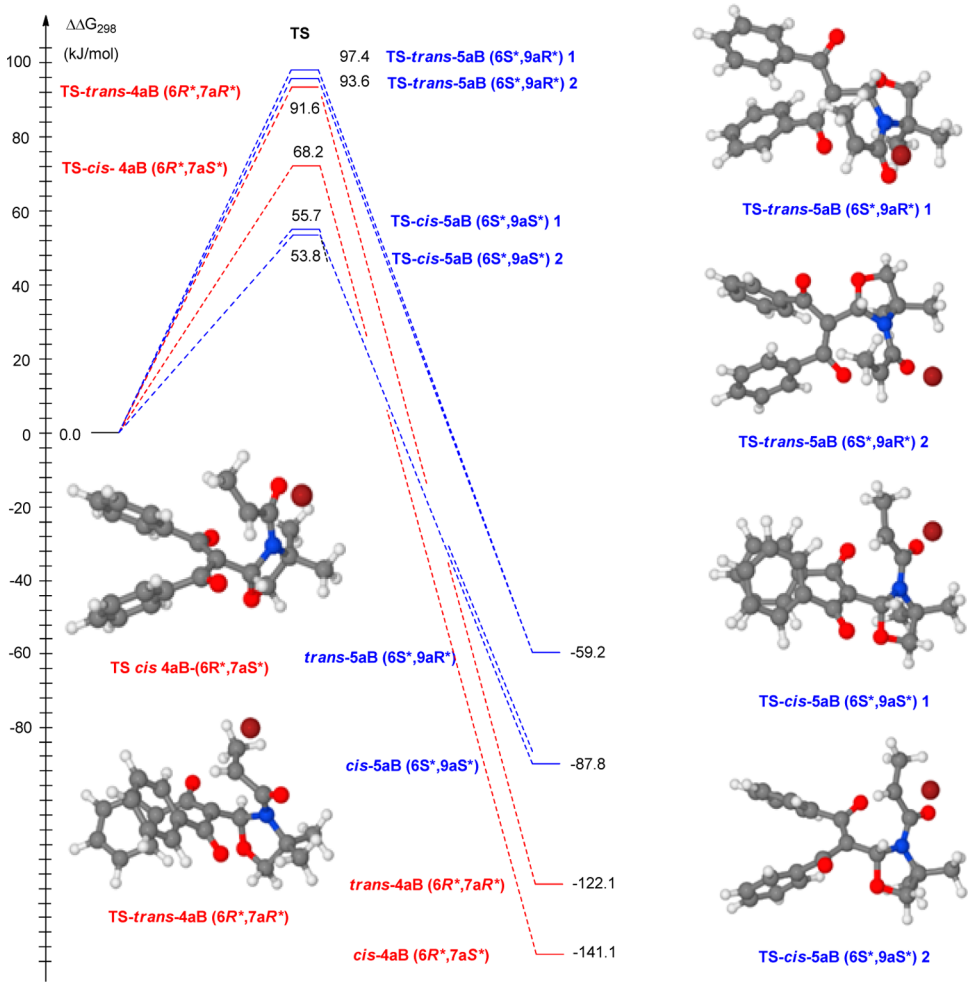

Figure 3. Last step of the reaction path to **4aB** and **5aB**. Gibbs free energies at 298 K in kJ/mol.

the aromatic ring and the specific shape of the phenyl group, the molecule tends to adopt a conformation in which the aromatic rings are on the same side and lead the oxygen of the carbonyl groups to be turned toward the electrophilic CH_2Br group and therefore favor its reactivity in *O*-alkylation. Due to the steric clash between the aromatic rings, in the transition state, the oxygen involved in the cyclization can either point upward (**TS-5aA-1**, Figure 2) or downward (**TS-5aA-2**, Figure 2) leading to two possible transition states for *O*-alkylation.

At this stage, the influence of the substitution on the carbon atom bearing the bromine was then studied by DFT at the same level. The influence of a methyl group at the α position of the amide (bromoamide **2B**) was studied considering both the steric effect and the diastereospecificity induced by this new chiral center. Interestingly, the presence of this substituent on the carbon bearing the bromine atom significantly decreased the energy barrier for the last step of the sequence from $\Delta G^{\ddagger}_{298}$ = 90 kJ/mol for **5aA** to $\Delta G^{\ddagger}_{298}$ = 54 kJ/mol for **5aB,** giving an explanation to the good yields observed experimentally with **2B**−**D** (Figure 3). It should also be noted that the energy gap existing between the two pathways (*O*- vs *C*-alkylation) increased compared to the previous case up to 14.4 kJ/mol, explaining the complete selectivity observed in this case in favor of the *O*-alkylation process. In addition, the total diastereoselectivity observed can be explained by the huge energy gap (almost 40 kJ/mol) existing between the transition states TS-*cis*-**5aB**-(6*S**,9a*S**) and TS-*trans*-**5aB**-(6*S**,9a*R**) (Figure 3) corresponding to the formation of the two possible diastereomers. Both the regio- and diastereoselective course of the sequence is therefore highly dependent on the steric bulk at the carbon atom bearing the bromine and its configuration. The presence of a substituent on this carbon is responsible of the preference for a reaction at the oxygen of the enolate, which is less bulky than the trisubstituted carbon. The diastereoselectivity is for its part mainly controlled by the position of the substituent in the transition state of the cyclization, which will point outside the ring in TS-*cis*-**5aB**-(6*S**,9a*S**) and inside for TS-*trans*-**5aB**-(6*S**,9a*R**).

The reaction with isopropyl ketones leading to the formation of **4bA** was also studied by DFT at the same level. The regioselectivity in favor of the *C*-alkylation product is mainly related to the specific conformation adopted by the keto−enolate **int-bA** (Figure 4). The conformation adopted places one of the isopropyl groups close to the oxazolidine inducing the CH_2Br to be placed right in front of the carbon of the enolate in the intermediate **Int-bA** (Figure 4). The *C*-alkylation process ($\Delta G^{\ddagger}_{298}$ = 75.5 kJ/mol) is hence favored over *O*-akylation by 4.1 kJ/mol in this case. This weak energy gap cannot completely explain why only **4bA** could be observed in this reaction. A small amount of **5bA** might be formed but the product could be poorly stable, explaining the modest yield observed (Table 1, entry 9).

In the case of unsymmetrical diketone derived Michael acceptors **1h** and **1i** bearing a CF_3 moiety, the desired 1,4-

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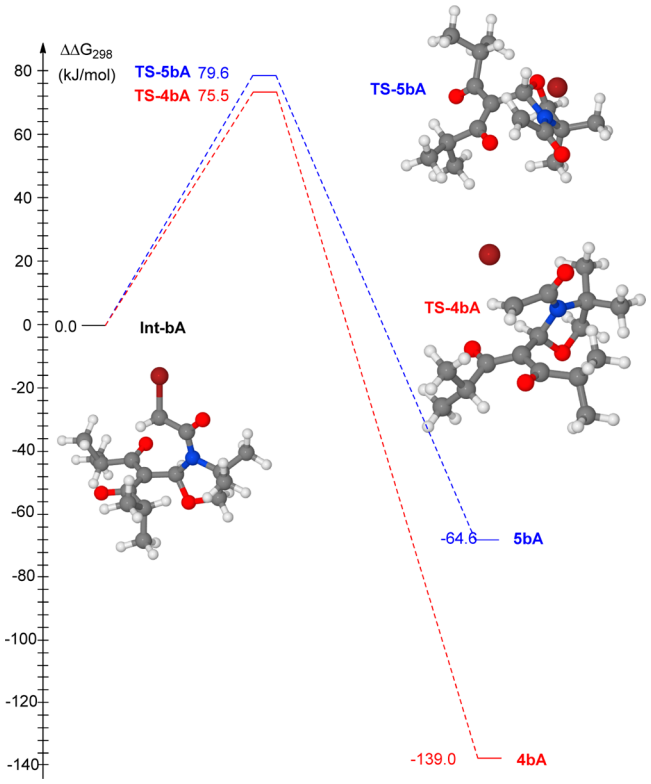
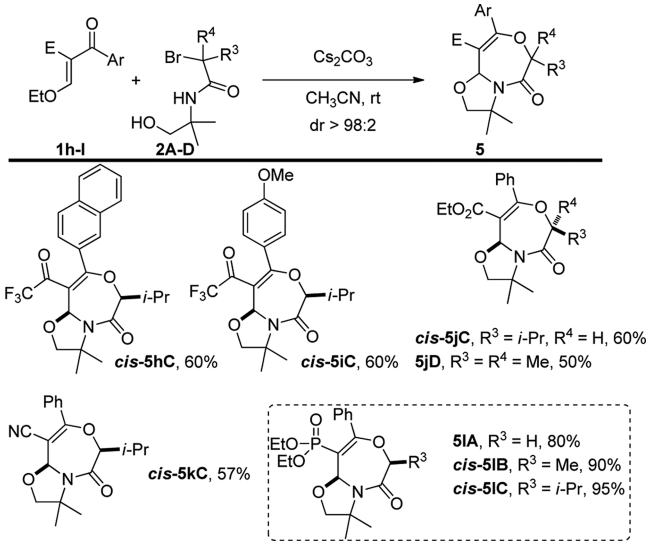


Figure 4. Last step of the reaction path to **4bA** and **5bA**. Gibbs free energies at 298 K in kJ/mol.

oxazepines *cis*-**5hC** and *cis*-**5iC** were thankfully isolated as the sole regioisomers (Scheme 4). Moreover, the process was

Scheme 4. Regioselective Synthesis of 1,4-Oxazepines 5

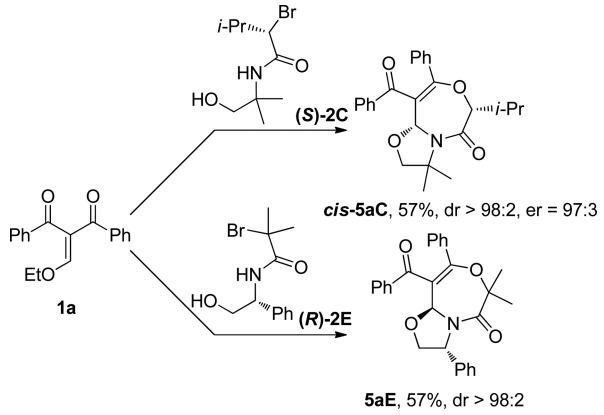


successfully extended to Michael acceptors **1j**, **1k**, and **1l** bearing, respectively, an ester, a nitrile, or even a phosphonate function. The latter proved to be an efficient partner allowing the formation of bicyclic systems *cis*-**5lA-C** in yields up to 95% even in the case of the more problematic hydroxyl α-bromoamides **2A** with 80% isolated yield (R^3 = R^4 = H). In this case the reaction was totally regioselective to *O*-alkylation.

The formation of **5lA** was also studied by DFT to rationalize the influence of the phosphonate group on the cyclization. In order to limit the computational cost, the corresponding methyl phosphonate **1l′** leading to **5l′A** was studied. *O*-alkylation was favored over *C*-alkylation process by 12.3 kJ/mol which corresponds to a significant increase in regioselectivity when compared to the selectivity calculated and observed for adducts **4aA** and **5aA**. In this case, the shape of the phosphonate displaying three oxygenated substituents pointing in all directions induces a slight increase in bulkiness around the carbon of the enolate and therefore disfavors the *C*-alkylation pathway compared to the *O*-alkylation pathway less influenced by the phosphonate (see **Int-l′A**, Figure 5). Most likely, in these reactions, not only the size, but also the shape of the substituents plays a key role in the regioselectivity.

Finally, the access to enantioenriched 1,4-oxazepines *cis*-**5aC** and **5aE** was then investigated in order to demonstrate the synthetic value of the present domino reaction (Scheme 5). In

Scheme 5. Synthesis of Enantioenriched 1,4-Oxazepines 5aE and 5aC



both cases, the bicyclic lactams, *cis*-**5aC** and **5aE**, were isolated in 57% yield with a diastereomeric ratio (dr) over 98:2. The structure of compound **5aE** was confirmed by single crystal X-ray diffraction (Figure 6).

CONCLUSION

In conclusion, we have introduced a new route to polysubstituted oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-ones through an efficient domino reaction. This domino oxa-Michael/aza-Michael/Williamson cycloetherification reaction is the first of its kind and gives access to a large diversity of highly functional structures. The starting materials are readily accessible and the procedure requires a very limited number of steps. With the help of DFT calculations, both the reactivity and the selectivity observed could be interpreted and give an overview of the scope and limitations of the method.

EXPERIMENTAL SECTION

All commercially available starting materials have been used without further purification. Compositions of stereoisomeric mixtures were determined by ^{1}H NMR analysis of the crude mixture before any purification. Melting points (mp) were taken with a SMP10 capillary melting point apparatus (Stuart) and are uncorrected. FT-IR spectra were recorded with a PerkinElmer Frontier. The NMR spectra were recorded on a 300 UltraShield instrument (Bruker) as solutions in $CDCl_3$ or CD_3CN at 300 MHz (^{1}H) and 75 MHz (^{13}C), respectively, and chemical shifts (δ) are expressed in ppm. High-resolution mass spectra were recorded on a 6530 Q-TOF (Agilent Technologies). Thin layer chromatography (TLC) was performed using silica gel

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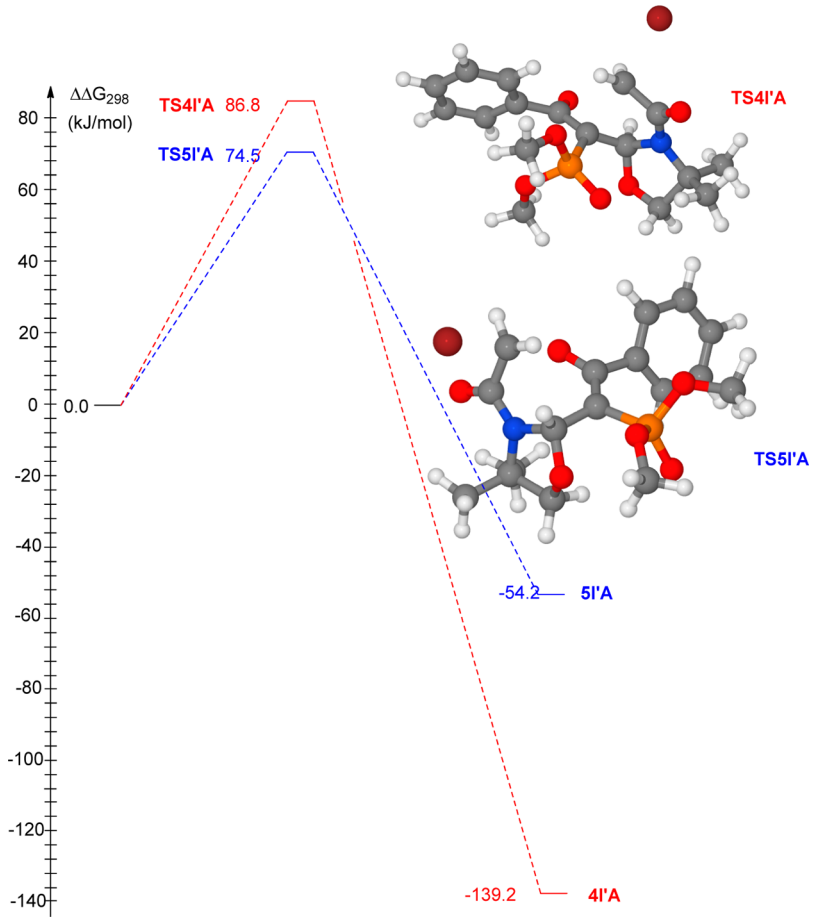

Figure 5. Last step of the reaction path to **4I′A** and **5I′A**. Gibbs free energies at 298 K in kJ/mol.

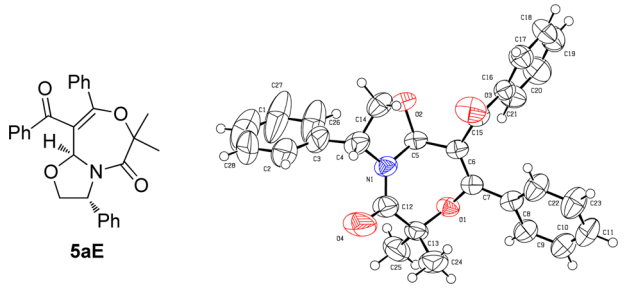

Figure 6. ORTEP of compound **5aE**.

analytical plates (*F*254) of 0.25 mm thickness. The detection on TLC plates was performed by UV light at 254 or 365 nm or using a permanganate revelator. Optical rotation were recorded on a 241 Polarimeter (PerkinElmer) in CH_2Cl_2 at 25 °C with $[\alpha]_D$ values reported in degrees and concentration (c) in g/mL. The Michael acceptors **1a−g** were prepared according to the literature procedures.[7] 2-Bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)acetamide **2A**, 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)propanamide **2B**, 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C**, 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-2-methylpropanamide **2D**, (*S*)-2-bromo-*N*-(1-hydroxy-2-methyl propan-2-yl)-3-methylbutanamide (*S*)-**2C**, and (*R*)-2-bromo-*N*-(2-hydroxy-1-phenylethyl)-2-methyl propanamide (*E*)-**2E** were prepared according to the literature procedures.[8]

General Procedure to Prepare 5a(A-D), 4aA, 4bA, 4cC, and 4bC. *Procedure A.* The required Michael acceptor **1** (0.25 mmol) and *N*-hydroxyalkyl-α- bromoacetamide **2** (0.3 mmol, 1.2 equiv) were dissolved in freshly distilled THF (2 mL). Sodium hydride (0.25 mmol, 1 equiv) was then added at 0 °C. The mixture was stirred for 3 to 5 h and was then quenched carefully at 0 °C by addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$ and solvent was removed under vacuum. The residue was then chromatographed on silica gel to provide the desired compound.

Procedure B. A solution of Michael acceptor **1** (0.25 mmol), *N*-hydroxyalkyl α-bromoacetamide **2** (0.3 mmol, 1.2 equiv), and cesium carbonate (0.25 mmol, 1 equiv) were dissolved in freshly distilled CH_3CN (2 mL). The resulting mixture was stirred for 12 h and was then quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated. The residue was then chromatographed on silica gel to give the desired compound.

(±)-(*S*)-9-Benzoyl-3,3-dimethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo- [3,2-*d*][1,4]oxazepin-5(3*H*)-one 5aA. Prepared from Michael acceptor **1a** (70.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)acetamide **2A** (63 mg, 1.2 equiv) following the general procedure B. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. 27 mg. Yield: 30%. R_f = 0.375 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 3H), 1.58 (s, 3H), 3.62 (d, J = 8.7 Hz, 1H), 3.77 (d, J = 8.7 Hz, 1H), 4.41 (d, J = 15.9 Hz, 1H), 4.81 (d, J = 15.8 Hz, 1H), 6.50 (s, 1H), 7.19−7.28 (m, 3H), 7.37−7.42 (m, 4H), 7.50−7.55 (m, 1H), 7.92 (dd, J = 7.2, 1.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.0, 61.5, 71.4, 78.6, 85.9, 126.2, 127.3 (2 x CH), 128.5 (2 x CH), 128.7 (2 x CH), 129.5 (2 x CH), 129.9, 132.2, 133.7, 137.0, 154.9, 165.2, 193.3 ppm; IR (neat): υ 1686, 1666, 1248, 944, 718, 689 cm^{-1}; HRMS (EI) m/z: calculated for $C_{22}H_{21}NO_4Na$ $[M+Na]^+$: 386.1360, found: 386.1365.

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(±)-(*S*)-7,7-Dibenzoyl-3,3-dimethyltetrahydropyrrolo[2,1-*b*]-oxazol-5(6*H*)-one 4aA. Prepared from Michael acceptor **1a** (70.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-acetamide **2A** (63 mg, 1.2 equiv) following the general procedure A. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. 58.1 mg. Yield: 64%. R_f = 0.37 (cyclohexane/EtOAc: 70/30); mp. 197−199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.58 (s, 3H), 2.82 (d, J = 16.7 Hz, 1H), 3.75 (d, J = 8.4 Hz, 1H), 3.78 (d, J = 16.7 Hz, 1H), 3.81 (d, J = 8.5 Hz, 1H), 6.66 (s, 1H), 7.27−7.33 (m, 4H), 7.37−7.46 (m, 2H), 7.63 (dd, J = 7.8, 1.6 Hz, 2H), 7.81 (dd, J = 7.7, 1.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 25.2, 44.4, 58.5, 65.5, 82.5, 93.7, 128.3 (2 x CH), 128.8 (2 x CH), 128.9 (2 x CH), 129.4 (2 x CH), 133.1, 133.7, 134.8, 137.1, 168.9, 194.6, 195.6; IR (neat): υ 1705, 1686, 1666, 1248, 943, 717, 689, 670 cm^{-1}; HRMS (EI) m/z: calculated for $C_{22}H_{21}NO_4Na$[M+Na] 386.1369, found 386.1369.

(±)-(6*S*,9a*S*)-9-Benzoyl-3,3,6-trimethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4] oxazepin-5(3*H*)-one *cis*-5aB. Prepared from Michael acceptor **1a** (70.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)propanamide **2B** (67.2 mg, 1.2 equiv) following the general procedure B. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. 81.1 mg. Yield: 86%. R_f = 0.425 (cyclohexane/EtOAc: 70/30); mp. 138−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, J = 6.2 Hz, 3H), 1.56 (s, 3H), 1.63 (s, 3H), 3.65 (d, J = 8.6 Hz, 1H), 3.80 (d, J = 8.6 Hz, 1H), 4.98 (q, J = 6.4 Hz, 1H), 6.66 (s, 1H), 7.12−7.17 (m, 3H), 7.28−7.33 (m, 4H), 7.39−7.45 (m, 1H), 7.81 (dd, J = 7.0, 1.5 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 23.3, 23.9, 61.6, 76.2, 78.3, 87.1, 116.1, 127.9 (2 x CH), 128.2 (2 x CH), 128.3 (2 x CH), 129.2, 129.3 (2 x CH), 132.9, 135.2, 137.7, 156.8, 165.1, 194.4 ppm; IR (neat): υ 1674, 1653, 1325, 1074, 883, 700 cm^{-1}; HRMS (EI) m/z: calculated for $C_{23}H_{24}NO_4$ [M+H]$^+$: 378.1705, found: 378.1692.

(±)-(6*S*,9a*S*)-9-Benzoyl-6-isopropyl-3,3-dimethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo- [3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5aC. Prepared from Michael acceptor **1a** (70.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure B. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. 86 mg. Yield: 85%. R_f = 0.625 (cyclohexane/EtOAc: 70/30); mp. 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.7 Hz, 6H), 1.56 (s, 3H), 1.63 (s, 3H), 2.41−2.48 (m, 1H), 3.65 (d, J = 8.6 Hz, 1H), 3.80 (d, J = 8.6 Hz, 1H), 4.32 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 7.10−7.15 (m, 3H), 7.24−7.31 (m, 4H), 7.37−7.43 (m, 1H), 7.79 (dd, J = 7.1, 4.1 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 19.3, 23.4, 23.9, 28.2, 61.5, 78.3, 84.6, 87.4, 115.3, 127.8 (2 x CH), 128.2 (2 x CH), 128.4 (2 x CH), 129.1, 129.3 (2 x CH), 132.8, 125.1, 137.8, 157.5, 164.2, 194.7 ppm; IR (neat): υ 1668, 1261, 1176, 730, 712 cm^{-1}; HRMS (EI) m/z: calculated for $C_{25}H_{28}NO_4$ [M+H]$^+$: 406.2018, found: 406.2016.

(±)-(*S*)-9-Benzoyl-3,3,6,6-tetramethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4] oxazepin-5(3*H*)-one 5aD. Prepared from Michael acceptor **1a** (70.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-2-methylpropanamide **2D** (71.4 mg, 1.2 equiv) following the general procedure B. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. 50 mg. Yield: 51%. R_f = 0.65 (cyclohexane/EtOAc: 70/30); mp. 161−163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.53 (s, 3H), 1.55 (s, 3H), 1.73 (s, 3H), 3.60 (d, J = 8.6 Hz, 1H), 3.80 (d, J = 8.6 Hz, 1H), 6.47 (s, 1H), 7.18−7.22 (m, 3H), 7.38−7.47 (m, 4H), 7.49−7.55 (m, 1H), 7.92 (dd, J = 7.1, 1.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 24.0, 25.4, 28.1, 61.7, 78.5, 85.0, 85.8, 126.6 (2 x CH), 128.3 (2 x CH), 128.7 (2 x CH), 129.3, 129.4 (2 x CH), 130.7, 133.7, 135.1, 136.9, 152.6, 170.6, 193.3 ppm; IR (neat): υ 1664, 1636, 1410, 1325, 908, 766 cm^{-1}; HRMS (EI) m/z: calculated for $C_{24}H_{26}NO_4$ [M+H]$^+$: 392.1845, found: 392.1845.

(±)-(*S*)-7,7-Bis(2-methylpropoyl)-3,3-dimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one 4bA. Prepared from Michael acceptor **1b** (53.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)acetamide **2A** (63 mg, 1.2 equiv) following the general procedure B. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. 44 mg. Yield: 60%. R_f = 0.225 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, J = 6.7 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H), 1.18 (t, J = 6.8 Hz, 6H), 1.38 (s, 3H), 1.52 (s, 3H), 2.74−2.89 (m, 2H), 2.86 (d, J = 16.7 Hz, 1H), 3.28 (d, J = 16.7 Hz, 1H), 3.83 (d, J = 8.6 Hz, 1H), 3.89 (d, J = 8.6 Hz, 1H), 5.77 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 19.5, 19.6, 20.0, 22.8, 25.3, 38.8, 39.2, 40.5, 58.1, 70.3, 82.9, 94.2, 169.1, 207.7, 209.9 ppm; IR (neat): υ 1709, 1693, 1405, 1096, 1071, 984, 962, 679 cm^{-1}; HRMS (EI) m/z: calculated for $C_{16}H_{26}NO_4$ [M+H]$^+$: 296.1866, found 296.1866.

(±)-(6*R*,7a*S*)-6-Isopropyl-7,7-diacetyl-3,3-dimethyltetrahydropyrro- lo[2,1-*b*]oxazol-5(6*H*)-one 4cC. Prepared from Michael acceptor **1c** (39 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure B. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. 43.4 mg. Yield: 75%. R_f = 0.35 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, J = 6.9 Hz, 3H), 1.23 (d, J = 6.4 Hz, 3H), 1.39 (s, 3H), 1.67 (s, 3H), 2.05−2.13 (m, 1H), 2.33 (s, 3H), 2.41 (s, 3H), 3.13 (d, J = 9.0 Hz, 1H), 3.87 (d, J = 8.5 Hz, 1H), 3.99 (d, J = 8.5 Hz, 1H), 5.25 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 22.2, 22.6, 25.8, 27.1, 28.7, 32.1, 55.7, 58.0, 74.9, 83.0, 92.3, 170.7, 202.7, 203.8 ppm; IR (neat): υ 1698, 1417, 1389, 1356, 1175, 1053, 802 cm^{-1}; HRMS (EI) m/z: calculated for $C_{15}H_{24}NO_4$ [M+H]$^+$: 282.1705, found 282.1701.

(±)-(6*R*,7a*S*)-6-Isopropyl-7,7-bis(2-methylpropoyl)-3,3-dimethyltetra hydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one 4bC. Prepared from Michael acceptor **1b** (53.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure B. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. 40.5 mg. Yield: 48%. R_f = 0.475 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 6.7 Hz, 3H), 1.21 (d, J = 6.5 Hz, 3H), 1.25 (d, J = 6.7 Hz, 3H), 1.38 (s, 3H), 1.54 (s, 3H), 2.26−2.38 (m, 1H), 2.74−2.81 (m, 1H), 2.75 (d, J = 8.2 Hz, 1H), 3.17−3.26 (m, 1H), 3.80 (d, J = 8.4 Hz, 1H), 3.84 (d, J = 8.4 Hz, 1H), 5.63 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 18.7, 19.1 (2 x CH_3), 21.0, 22.3, 22.7, 25.3, 26.6, 39.8, 41.3, 57.7, 61.3, 74.3, 83.3, 93.4, 170.5, 209.1, 211.1 ppm; IR (neat): υ 1709, 1407, 1367, 1385, 1072, 929, 804 cm^{-1}; HRMS (EI) m/z: calculated for $C_{19}H_{32}NO_4$ [M+H]$^+$: 338.2333, found 338.2333.

General Procedure To Prepare 5(d-f)C, 5g(B-D), 5′(d-f)C, and 5′g(B-D). A solution of Michael acceptor **1** (0.25 mmol), *N*-hydroxyalkyl α-bromoacetamide **2** (0.3 mmol, 1.2 equiv), and cesium carbonate (0.25 mmol, 1 equiv) were dissolved in freshly distilled CH_3CN (2 mL). The resulting mixture was stirred for 12 h and was then quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$ and evaporated. The residue was then chromatographed on silica gel to give the desired compounds **5** and **5′**. The regioisomers **5** and **5′** were determined by 2D HMBC, ^{1}H NMR and ^{13}C NMR techniques.

(±)-(6*S*,9a*S*)-9-Benzoyl-8-(3,4-dimethoxyphenyl)-6-isopropyl-3,3-dimethyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5dC. Prepared from Michael acceptor **1d** (85.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. 48.9 mg. Yield: 42%. R_f = 0.375 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 5.1 Hz, 3H), 1.09 (d, J = 5.1 Hz, 3H), 1.56 (s, 3H), 1.63 (s,

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3H), 2.41−2.52 (m, 1H), 3.64 (d, J = 8.6 Hz, 1H), 3.74 (s, 3H), 3.76 (s, 3H), 3.80 (d, J = 8.6 Hz, 1H), 4.30 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.64 (s, 1H), 6.84 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 8.3, 2.0 Hz, 1H), 7.30 (t, J = 7.4 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.81 (dd, J = 7.1, 1.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 19.3, 23.4, 23.9, 28.2, 55.7, 55.8, 61.5, 78.3, 84.5, 87.4, 110.2, 111.5, 114.5, 121.7, 127.8, 128.3 (2 x CH), 129.3 (2 x CH), 132.9, 137.9, 148.1, 149.6, 157.0, 164.4, 194.9 ppm; IR (neat): υ 1709, 1668, 1598, 1515, 1265, 1220, 1175, 1023, 725 cm^{-1}; HRMS (EI) m/z: calculated for $C_{27}H_{32}NO_6$ $[M+H]^+$: 466.2229, found 466.2210.

(±)-(6*S*,9a*S*)-9-(3,4-Dimethoxybenzoyl)-6-isopropyl-3,3-dimethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]-oxazepin-5(3*H*)-one *cis*-5′dC. Prepared from Michael acceptor **1d** (85.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. 55.9 mg. Yield: 48%. R_f = 0.25 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, J = 6.6 Hz, 6H), 1.55 (s, 3H), 1.62 (s, 3H), 2.34−2.49 (m, 1H), 3.64 (d, J = 8.5 Hz, 1H), 3.78 (d, J = 8.6 Hz, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 4.30 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.72 (d, J = 8.4 Hz, 1H), 7.11−7.16 (m, 3H), 7.30−7.33 (m, 2H), 7.36 (d, J = 1.9 Hz, 1H), 7.43 (dd, J = 8.4, 2.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 19.3, 23.3, 23.9, 28.2, 55.8, 56.0, 61.5, 78.4, 84.5, 87.5, 109.7, 110.9, 115.0, 124.8, 127.9 (2 x CH), 128.1 (2 x CH), 129.1, 130.8, 135.3, 148.7, 153.2, 156.6, 164.3, 193.4 ppm; IR (neat): υ 1655, 1583, 1512, 1328, 1266, 1173, 1020, 768, 697 cm^{-1}; HRMS (EI) m/z: calculated for $C_{27}H_{32}NO_6$ $[M+H]^+$: 466.2181, found 466.2202.

(±)-(6*S*,9a*S*)-9-Benzoyl-6-isopropyl-3,3-dimethyl-8-(thiophen-2-yl)-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5eC. Prepared from Michael acceptor **1e** (71.6 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 41 mg. Yield: 40%. R_f = 0.5 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, J = 6.7 Hz, 3H), 1.21 (d, J = 6.7 Hz, 3H), 1.52 (s, 3H), 1.61 (s, 3H), 2.44−2.56 (m, 1H), 3.65 (d, J = 8.6 Hz, 1H), 3.83 (d, J = 8.6 Hz, 1H), 4.35 (d, J = 8.0 Hz, 1H), 6.58 (s, 1H), 6.77 (dd, J = 5.1, 3.8 Hz, 1H), 7.09 (dd, J = 3.8, 1.0 Hz, 1H), 7.24 (dd, J = 5.1, 1.1 Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 7.49−7.55 (m, 1H), 7.93 (dd, J = 7.1, 1.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 19.5, 23.5, 23.6, 28.4, 61.5, 78.4, 84.8, 86.9, 114.4, 126.8, 127.8, 128.6 (2 x CH), 129.3 (2 x CH), 129.3, 133.3, 136.7, 137.4, 150.4, 164.1, 193.8 ppm; IR (neat): υ 1775, 1709, 1669, 1597, 1387, 1255, 1177, 1092, 910, 727 cm^{-1}; HRMS (EI) m/z: calculated for $C_{23}H_{26}NO_4S$ $[M+H]^+$: 412.1582, found 412.1566.

(±)-(6*S*,9a*S*)-6-Isopropyl-3,3-dimethyl-8-phenyl-9-(thiophene-2-carbonyl)-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]-oxazepin-5(3*H*)-one *cis*-5′eC. Prepared from Michael acceptor **1e** (71.6 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 47.3 mg. Yield: 46%. R_f = 0.575 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H), 1.56 (s, 3H), 1.62 (s, 3H), 2.39−3.51 (m, 1H), 3.70 (d, J = 8.6 Hz, 1H), 3.87 (d, J = 8.6 Hz, 1H), 4.30 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 6.91 (dd, J = 4.8, 3.9 Hz, 1H), 7.16−7.20 (m, 3H), 7.37−7.40 (m, 2H), 7.45 (dd, J = 3.8, 1.1 Hz, 1H), 7.49 (dd, J = 4.9, 1.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 19.3, 23.4, 23.8, 28.2, 61.6, 78.5, 84.6, 87.1, 115.9, 127.8, 127.9 (2 x CH), 128.3 (2 xCH), 129.3, 133.7, 134.2, 135.3, 145.4, 157.6, 164.1, 186.5 ppm; IR (neat): υ 1671, 1636, 1411, 1266, 1175, 1075, 909, 772, 726, 697 cm^{-1}; HRMS (EI) m/z: calculated for $C_{23}H_{26}NO_4S$ $[M+H]^+$: 412.1568, found 412.1580.

(±)-(6*S*,9a*S*)-9-Benzoyl-6-isopropyl-3,3-dimethyl-8-(pyridin-3-yl)-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5fC. Prepared from Michael acceptor **1f** (70.3 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. 38.6 mg. Yield: 38%. R_f = 0.28 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.7 Hz, 6H), 1.56 (s, 3H), 1.64 (s, 3H), 2.39−2.51 (m, 1H), 3.66 (d, J = 8.7 Hz, 1H), 3.81 (d, J = 8.6 Hz, 1H), 4.33 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 7.10 (dd, J = 7.4, 4.9 Hz, 1H), 7.31−7.37 (m, 2H), 7.42−7.48 (m, 1H), 7.63−7.67 (m, 1H), 7.80 (dd, J = 7.0, 1.5 Hz, 2H), 8.40 (dd, J = 4.8, 1.3 Hz, 1H), 8.54 (d, J = 1.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 19.3, 23.4, 23.9, 28.2, 61.7, 78.3, 84.9, 87.1, 117.2, 122.7, 128.6 (2 x CH), 129.2 (2 x CH), 131.1, 133.3, 135.9, 137.6, 149.0, 150.1, 154.6, 163.9, 193.8 ppm; IR (neat): υ 1677, 1658, 1337, 1280, 1076, 1007, 890, 708 cm^{-1}; HRMS (EI) m/z: calculated for $C_{24}H_{27}N_2O_4$ $[M+H]^+$: 407.1974, found 407.1971.

(±)-(6*S*,9a*S*)-6-Isopropyl-3,3-dimethyl-9-nicotinoyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5′fC. Prepared from Michael acceptor **1f** (70.3 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. 32.5 mg. Yield: 32%. R_f = 0.25 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, J = 2.0 Hz, 3H), 1.07 (d, J = 1.9 Hz, 3H), 1.58 (s, 3H), 1.64 (s, 3H), 2.39−2.51 (m, 1H), 3.67 (d, J = 8.7 Hz, 1H), 3.81 (d, J = 8.7 Hz, 1H), 4.29 (d, J = 8.5 Hz, 1H), 6.65 (s, 1H), 7.13−7.15 (m, 3H), 7.21 (dd, J = 7.9, 4.9 Hz, 1H), 7.25−7.27 (m, 2H), 7.99 (dt, J = 7.9, 1.8 Hz, 1H), 8.56 (d, J = 3.6 Hz, 1H), 8.94 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 19.2, 23.3, 24.0, 28.2, 61.7, 78.3, 84.8, 87.3, 114.7, 123.2, 128.1 (2 x CH), 128.4 (2 x CH), 129.5, 133.3, 134.7, 136.0, 150.8, 152.8, 158.8, 164.0, 193.6 ppm; IR (neat): υ 1678, 1630, 1585, 1336, 1193, 772 cm^{-1}; HRMS (EI) m/z: calculated for $C_{24}H_{27}N_2O_4$ $[M+H]^+$: 407.1963, found 407.1972.

(±)-(6*S*,9a*S*)-9-Benzoyl-8-(2-methoxypyridin-3-yl)-3,3,6-trimethyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5gB. Prepared from Michael acceptor **1g** (77.8 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)propanamide **2B** (67.2 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 35.7 mg. Yield: 35%. R_f = 0.275 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ1.52 (d, J = 6.4 Hz, 3H), 1.54 (s, 3H), 1.65 (s, 3H), 3.65 (d, J = 8.6 Hz, 1H), 3.75 (s, 3H), 3.82 (d, J = 8.6 Hz, 1H), 4.97 (q, J = 6.4 Hz, 1H), 6.64 (s, 1H), 6.73 (dd, J = 7.3, 5.1 Hz, 1H), 7.35 (t, J = 7.4 Hz, 2H), 7.44−7.51 (m, 2H), 7.81 (dd, J = 7.1, 1.4 Hz, 2H), 7.98 (dd, J = 5.0, 1.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 23.4, 23.7, 53.1, 61.6, 76.6, 78.2, 86.9, 115.9, 118.0, 118.6, 128.2 (2 x CH), 128.8 (2 x CH), 132.8, 138.0, 139.2, 147.8, 154.4, 160.2, 164.9, 193.5 ppm; IR (neat): υ 1671, 1580, 1465, 1404, 1255, 1077, 690 cm^{-1}; HRMS (EI) m/z: calculated for $C_{23}H_{25}N_2O_5$ $[M+H]^+$: 409.1741, found 409.1745.

(±)-(6*S*,9a*S*)-9-(2-Methoxynicotinoyl)-3,3,6-trimethyl-8-phenyl-6,9a-dihydro-2*H*-oxazo- lo[3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5′gB. Prepared from Michael acceptor **1g** (77.8 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)propanamide **2B** (67.2 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 40.8 mg. Yield: 40%. R_f = 0.225 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, J = 7.3 Hz, 3H), 1.56 (s, 3H), 1.63 (s, 3H), 3.71 (d, J = 8.5 Hz, 1H), 3.90 (d, J = 8.5 Hz, 1H), 3.99 (s, 3H), 4.94 (q, J = 6.4 Hz, 1H), 6.61 (s, 1H), 6.78 (dd, J = 7.5, 4.9 Hz, 1H), 7.13−7.18 (m, 3H), 7.24−7.27 (m, 2H), 7.80 (dd, J = 7.5, 2.0 Hz, 1H), 8.10 (dd, J = 4.9, 2.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 23.4, 23.6, 53.7, 61.5, 76.5, 78.2, 87.1, 116.7, 118.6, 122.9, 127.7 (2 x CH), 128.7 (2 x CH), 129.5, 135.2, 140.3, 150.2, 159.7, 160.7, 165.0, 191.8 ppm; IR (neat): υ 1670, 1578, 1465, 1404, 1267, 1079, 670 cm^{-1}; HRMS (EI) m/z: calculated for $C_{23}H_{25}N_2O_5$ $[M+H]^+$: 409.1745, found 409.1745.

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(±)-(6*S*,9a*S*)-9-Benzoyl-6-isopropyl-8-(2-methoxypyridin-3-yl)-3,3-dimethyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5gC. Prepared from Michael acceptor **1g** (77.8 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 59 mg. Yield: 54%. R_f = 0.375 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H), 1.55 (s, 3H), 1.66 (s, 3H), 2.34−2.45 (m, 1H), 3.66 (d, J = 8.6 Hz, 1H), 3.78 (s, 3H), 3.84 (d, J = 8.6 Hz, 1H), 4.30 (d, J = 8.7 Hz, 1H), 6.64 (s, 1H), 6.74 (dd, J = 7.3, 5.1 Hz, 1H), 7.36 (t, J = 7.4 Hz, 2H), 7.44−7.51 (m, 2H), 7.80 (dd, J = 7.0, 1.5 Hz, 2H), 7.99 (dd, J = 5.1, 1.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 19.2, 23.5, 23.7, 28.1, 53.2, 61.5, 78.3, 85.1, 87.0, 115.9, 117.9, 118.3, 128.2 (2 x CH), 128.8 (2 x CH), 132.8, 138.1, 139.7, 147.7, 154.8, 160.4, 164.1, 193.6 ppm; IR (neat): υ 1672, 1580, 1465, 1404, 1242, 1013, 693 cm^{-1}; HRMS (EI) m/z: calculated for $C_{25}H_{29}N_2O_5$ $[M+H]^+$: 437.2076, found 437.2050.

(±)-(6*S*,9a*S*)-6-Isopropyl-9-(2-methoxynicotinoyl)-3,3-dimethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]-oxazepin-5(3*H*)-one *cis*-5′gC. Prepared from Michael acceptor **1g** (77.8 mg, 0.25 mmol) and 2-bromo-N-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 38 mg. Yield: 35%. R_f = 0.4 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, J = 6.5 Hz, 3H), 1.11 (d, J = 6.1 Hz, 3H), 1.56 (s, 3H), 1.63 (s, 3H), 2.39−2.51 (m, 1H), 3.73 (d, J = 8.5 Hz, 1H), 3.93 (d, J = 8.5 Hz, 1H), 4.00 (s, 3H), 4.32 (d, J = 8.5 Hz, 1H), 6.62 (s, 1H), 6.78 (dd, J = 7.5, 4.9 Hz, 1H), 7.16−7.21 (m, 2H), 7.26−7.27 (m, 3H), 7.76 (dd, J = 7.5, 2.0 Hz, 1H), 8.10 (dd, J = 4.9, 2.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 19.5, 23.5, 23.6, 28.1, 53.7, 61.4, 78.3, 85.1, 87.2, 116.8, 118.3, 123.2, 127.6 (2 x CH), 129.0 (2 x CH), 129.5, 135.1, 140.2, 150.1, 160.4, 160.6, 164.1, 191.7 ppm; IR (neat): υ 1674, 1581, 1464, 1404, 1248, 1009, 771, 697 cm^{-1}; HRMS (EI) m/z: calculated for $C_{25}H_{29}N_2O_5$ $[M+H]^+$: 437.2054, found 437.2065.

(±)-(*S*)-9-(2-Methoxynicotinoyl)-3,3,6,6-tetramethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-one 5′gD and (±)-(*S*)-9-Benzoyl-8-(2-methoxy- pyridin-3-yl)-3,3,6,6-tetramethyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]-oxazepin-5(3*H*)-one 5gD. Prepared from Michael acceptor **1g** (77.8 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-2-methylpropanamide **2D** (71.4 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 58 mg. Yield: 55%. R_f = 0.475 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 1.62H), 1.39 (s, 3H), 1.52 (s, 3H), 1.53 (s, 3.24H), 1.57 (s, 3H), 1.68 (s, 3H), 1.69 (s, 1.62H), 3.43 (s, 3H), 3.57 (d, J = 8.6 Hz, 1H), 3.62 (d, J = 8.3 Hz, 0.54H), 3.74 (d, J = 8.6 Hz, 1H), 3.80 (d, J = 8.5 Hz, 0.54H), 3.97 (s, 1.62H), 6.40 (s, 1H), 6.41 (s, 0.54H), 6.84 (dd, J = 7.5, 5.0 Hz, 1H), 6.90 (dd, J = 7.5, 4.9 Hz, 0.54H), 7.19−7.21 (m, 1.62H), 7.36−7.41 (m, 3.8H), 7.47−7.52 (m, 1H), 7.76 (dd, J = 7.5, 1.9 Hz, 1H), 7.87 (dd, J = 8.4, 1.4 Hz, 2H), 8.02 (dd, J = 5.0, 1.9 Hz, 1H), 8.07 (dd, J = 7.5, 2.0 Hz, 0.54H), 8.23 (dd, J = 4.9, 2.0 Hz, 0.54H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 23.4, 23.8, 24.2, 25.1, 25.5, 27.7, 28.1, 52.2, 54.2, 61.7, 62.0, 78.5, 78.6, 84.8, 85.0, 85.8, 85.9, 116.4, 116.8, 119.2, 121.5, 126.8 (2 x CH), 128.1 (2 x CH), 128.2 (2 x CH), 129.1, 129.3 (2 x CH), 131.2, 132.9, 133.0, 135.5, 137.6, 138.0, 140.6, 147.6, 150.3, 151.4, 152.4, 159.3, 162.1, 170.6, 170.7, 191.0, 191.9 ppm; IR (neat): υ 1643, 1578, 1465, 1405, 1295, 1198, 1012, 909, 691 cm^{-1}; HRMS (EI) m/z: calculated for $C_{24}H_{27}N_2O_5$ $[M+H]^+$: 423.1905, found 423.1905.

General Procedure To Prepare 5(h-l)C, 5jD, 5lA, and 5lB. A solution of Michael acceptor **1** (0.25 mmol), *N*-hydroxyalkyl α-bromoacetamide **2** (0.3 mmol, 1.2 equiv) and cesium carbonate (0.25 mmol, 1 equiv) were dissolved in freshly distilled CH_3CN (2 mL). The resulting mixture was stirred for 5 to 12 h and was then quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated. The residue was then chromatographed on silica gel to give the desired compound.

(±)-(6*S*,9a*S*,*E*)-6-Isopropyl-3,3-dimethyl-8-(naphthalen-2-yl)-9-(2,2,2-trifluoroacetyl)-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]-oxazepin-5(3*H*)-one *cis*-5hC. Prepared from Michael acceptor **1h** (80.6 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 67 mg. Yield: 60%. R_f = 0.575 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H), 1.52 (s, 3H), 1.63 (s, 3H), 2.43−2.54 (m, 1H), 3.57 (d, J = 8.5 Hz, 1H), 3.69 (d, J = 7.3 Hz, 1H), 4.25 (d, J = 8.1 Hz, 1H), 6.56 (s, 1H), 7.58−7.69 (m, 2H), 7.92−8.06 (m, 4H), 8.43 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 19.2, 23.2, 23.7, 28.3, 61.8, 78.5, 85.5, 86.6, 119.3 (q, J = 276.7 Hz), 119.6 (q, J = 6.7 Hz), 124.0, 124.8, 127.0, 127.9, 128.8, 129.0, 131.9, 132.4, 134.4, 136.0, 141.3, 163.6, 175.4 (q, J = 38.9 Hz) ppm; IR (neat): υ 1659, 1626, 1355, 1287, 1192, 1146, 1012, 789 cm^{-1}; HRMS (EI) m/z: calculated for $C_{24}H_{25}F_3NO_4$ $[M+H]^+$: 448.1728, found 448.1729.

(±)-(6*S*,9a*S*)-6-Isopropyl-8-(4-methoxyphenyl)-3,3-dimethyl-9-(2,2,2-trifluoroacetyl)-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]-oxazepin-5(3*H*)-one *cis*-5iC. Prepared from Michael acceptor **1i** (75.6 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 64 mg. Yield: 60%. R_f = 0.5 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H), 1.51 (s, 3H), 1.59 (s, 3H), 2.38−2.50 (m, 1H), 3.60 (d, J = 7.5 Hz, 1H), 3.66 (d, J = 7.5 Hz, 1H), 3.90 (s, 3H), 4.18 (d, J = 7.5 Hz, 1H), 6.48 (s, 1H), 6.99 (d, J = 8.9 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 19.2, 23.2, 23.6, 28.2, 55.6, 61.8, 78.4, 85.5, 86.7, 114.0 (2 x CH), 114.2 (q, J = 7.2 Hz), 119.3 (q, J = 276.3 Hz), 131.6 (2 x CH), 131.8, 143.3 (q, J = 11 Hz), 160.6, 164.2, 179.2 (q, J = 35.4 Hz) ppm; IR (neat): υ 1658, 1599, 1256, 1130, 886 cm^{-1}; HRMS (EI) m/z: calculated for $C_{21}H_{25}F_3NO_5$ $[M+H]^+$: 428.1669, found 428.1683.

(±)-(6*S*,9a*S*)-9-Ethoxycarbonyl-6-isopropyl-3,3-dimethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5jC. Prepared from Michael acceptor **1j** (62.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 56 mg. Yield: 60%. R_f = 0.575 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H), 1.56 (s, 3H), 1.58 (s, 3H), 2.35−2.45 (m, 1H), 3.78 (d, J = 8.5 Hz, 1H), 3.92 (d, J = 8.5 Hz, 1H), 3.98 (qd, J = 7.1, 1.0 Hz, 2H), 4.20 (d, J = 8.6 Hz, 1H), 6.50 (s, 1H), 7.28−7.39 (m, 3H), 7.43 (dd, J = 7.7, 1.8 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 17.0, 19.3, 23.4, 23.6, 28.0, 60.8, 61.7, 78.3, 85.1, 86.5, 110.9, 127.7 (2 x CH), 128.7 (2 x CH), 129.6, 135.4, 161.0, 164.0, 166.3 ppm; IR (neat): υ 1714, 1678, 1264, 1177, 1050, 698 cm^{-1}; HRMS (EI) m/z: calculated for $C_{21}H_{28}NO_5$ $[M+H]^+$: 374.1967, found 374.1962.

(±)-(*S*)-9-Ethoxycarbonyl-3,3,6,6-tetramethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*] [1,4] oxazepin-5(3*H*)-one 5jD. Prepared from Michael acceptor **1j** (62.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-2-methylpropanamide **2D** (71.4 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. 45 mg. Yield: 50%. R_f = 0.612 (cyclohexane/EtOAc: 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ1.22 (t, J = 7.1 Hz, 3H), 1.30 (s, 3H), 1.54 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 3.71 (d, J = 8.5 Hz, 1H), 3.96 (d, J = 8.5 Hz, 1H), 4.24 (qd, J = 7.1, 2.5 Hz, 2H), 6.28 (s, 1H), 7.34−7.38

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(m, 3H), 7.52 (dd, J = 6.7, 3.1 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 23.2, 23.8, 25.5, 27.7, 61.4, 61.8, 78.5, 84.8, 84.9, 125.6, 126.4 (2 x CH), 128.3 (2 x CH), 129.5, 135.3, 154.1, 165.2, 170.3 ppm; IR (neat): υ 1725, 1645, 1196, 1155, 1055, 1012, 698 cm^{-1}; HRMS (EI) m/z: calculated for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1803, found 360.1808.

(±)-(6*S*,9a*S*)-9-Cyano-6-isopropyl-3,3-dimethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-5(3*H*)-one *cis*-5kC. Prepared from Michael acceptor **1k** (50.3 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. 46 mg. Yield: 57%. R_f = 0.55 (cyclohexane/EtOAc: 70/30); mp. 159−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, J = 6.7 Hz, 3H), 1.22 (d, J = 6.7 Hz, 3H), 1.57 (s, 6H), 2.47−2.58 (m, 1H), 3.90 (d, J = 8.7 Hz, 1H), 4.02 (d, J = 8.7 Hz, 1H), 4.26 (d, J = 8.4 Hz, 1H), 6.30 (s, 1H), 7.43−7.55 (m, 3H), 7.71 (dd, J = 6.9, 1.5 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 19.3, 23.5, 23.5, 28.2, 62.1, 78.6, 84.5, 85.7, 90.2, 117.1, 128.5 (2 x CH), 128.9 (2 x CH), 131.8, 133.2, 162.7, 170.6 ppm; IR (neat): υ 2204, 1676, 1594, 1333, 1268, 1089, 778, 705 cm^{-1}; HRMS (EI) m/z: calculated for $C_{19}H_{22}N_2O_3$ $[M+H]^+$: 327.1708, found 327.1696.

(±)-(*S*)-Diethyl 3,3-Dimethyl-5-oxo-8-phenyl-3,5,6,9a-tetrahydro-2*H*-oxazolo[3,2-*d*][1,4] -oxazepin-9-ylphosphonate 5lA. Prepared from Michael acceptor **1l** (78.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)acetamide **2A** (63 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 79 mg. Yield: 80%. R_f = 0.175 (cyclohexane/EtOAc: 0/100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H), 1.55 (s, 6H), 3.65−3.73 (m, 1H), 3.80−3.91 (m, 2H), 3.84 (d, J = 8.6 Hz, 1H), 3.94−4.01 (m, 1H), 4.00 (d, J = 8.5 Hz, 1H), 4.48 (d, J = 12.8 Hz, 1H), 4.76 (d, J = 12.8 Hz, 1H), 6.34 (d, J = 2.2 Hz, 1H), 7.37−7.50 (m, 3H), 7.63 (dd, J = 6.8, 1.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 16.0, 23.0, 23.4, 61.6, 61.7 (d, J = 7.0 Hz), 62.0 (d, J = 6.1 Hz), 73.4, 77.9, 87.4 (d, J = 7.3 Hz), 105.2 (d, J = 196.3 Hz), 127.8 (2 x CH), 130.0 (2 x CH), 131.0, 135.9 (d, J = 3.0 Hz), 164.1, 169.2 (d, J = 19.4 Hz) ppm; IR (neat): υ 1681, 1592, 1367, 1237, 1020, 971, 770, 698 cm^{-1}; HRMS (EI) m/z: calculated for $C_{19}H_{27}NO_6P$ $[M+H]^+$: 396.1576, found 396.1575.

(±)-Diethyl (6*S*,9a*S*)-3,3,6-Trimethyl-5-oxo-8-phenyl-3,5,6,9a-tetrahydro-2*H*-oxazolo[3,2-*d*] [1,4]oxazepin-9-yl-phosphonate *cis*-5lB. Prepared from Michael acceptor **1l** (78.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-propanamide **2B** (67.2 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 92 mg. Yield: 90%. R_f = 0.2 (cyclohexane/EtOAc: 0/100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.1 Hz, 3H), 1.50 (s, 3H), 1.51 (s, 3H), 1.54 (d, J = 6.4 Hz, 3H), 3.59−3.68 (m, 1H), 3.78−3.89 (m, 2H), 3.83 (d, J = 8.5 Hz, 1H),3.90−4.03 (m, 1H), 3.97 (d, J = 8.7 Hz, 1H), 4.79 (q, J = 6.4 Hz, 1H), 6.35 (d, J = 1.2 Hz, 1H), 7.34−7.45 (m, 3H), 7.60 (dd, J = 6.8, 1.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 15.9 (d, J = 3.2 Hz), 16.0 (d, J = 3.6 Hz), 22.9, 23.5, 61.6 (d, J = 6.4 Hz), 61.6, 62.0 (d, J = 6.2 Hz), 77.3, 77.8, 87.6 (d, J = 7.7 Hz), 103.7 (d, J = 197.5 Hz), 127.8 (2 x CH), 129.9 (2 x CH), 130.9, 136.2 (d, J = 3.1 Hz), 165.1, 169.2, 169.3 (d, J = 19.9 Hz) ppm; IR (neat): υ 1678, 1590, 1382, 1224, 1050, 1021, 969, 729, 699 cm^{-1}; HRMS (EI) m/z: calculated for: $C_{20}H_{29}NO_6P$ $[M+H]^+$: 410.1719, found 410.1724.

(±)-Diethyl (6*S*,9a*S*)-6-Isopropyl-3,3-dimethyl-5-oxo-8-phenyl-3,5,6,9a-tetrahydro-2*H*-oxazolo[3,2-*d*][1,4]oxazepin-9-yl-phosphonate *cis*-5lC. Prepared from Michael acceptor **1l** (78.1 mg, 0.25 mmol) and 2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide **2C** (75.6 mg, 1.2 equiv) following the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. 103.8 mg. Yield: 95%. R_f = 0.35 (cyclohexane/EtOAc: 0/100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 1.17 (d, J = 6.7 Hz, 3H), 1.50 (s, 3H), 1.51 (s, 3H), 2.39−2.50 (m, 1H), 3.54−3.68 (m, 1H), 3.78−3.88 (m, 1H), 3.83 (d, J = 8.4 Hz, 1H), 3.92−3.40 (m, 2H), 3.99 (d, J = 8.3 Hz, 1H), 4.17 (d, J = 8.6 Hz, 1H), 6.37 (d, J = 1.1 Hz, 1H), 7.34−7.45 (m, 3H), 7.59 (dd, J = 6.8, 1.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 16.0 (d, J = 1.3 Hz), 18.2, 19.4, 23.0, 23.7, 27.9, 61.55 (d, J = 6.3 Hz), 61.6, 62.0 (d, J = 6.2 Hz), 77.8, 85.5, 87.53 (d, J = 7.6 Hz), 103.94 (d, J = 197.7 Hz), 127.9 (2 x CH), 129.8 (2 x CH), 130.8, 136.6 (d, J = 3.2 Hz), 164.0, 169.7 (d, J = 20.2 Hz) ppm; IR (neat): υ 1679, 1575, 1230, 1051, 1024, 968, 729 cm^{-1}; HRMS (EI) m/z: calculated for $C_{22}H_{33}NO_6P$ $[M+H]^+$: 438.2053, found 438.2047.

Preparation of (*R*,*R*)-*cis*-5aC and (*S*,*R*)-5aE. *Procedure To Prepare (R,R)-cis-5aC.* The required Michael acceptor **1a** (70.1 mg, 0.25 mmol) and (*S*)-2-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide (*S*)-**2C** (*S*)-**2C** (75.6 mg, 1.2 equiv) were dissolved in freshly distilled THF (2 mL). Sodium hydride (0.25 mmol, 1 equiv) was then added at 0 °C. The mixture was stirred for 3 to 5 h and was then quenched carefully at 0 °C by addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$ and solvent was removed under vacuum. The residue was then chromatographed on silica gel to provide the desired compound (*R*,*R*)-*cis*-**5aC**.

(6*R*,9a*R*)-9-Benzoyl-6-isopropyl-3,3-dimethyl-8-phenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*] [1,4]oxazepin-5(3*H*)-one (*R*,*R*)-*cis*-5aC. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. 58 mg. Yield: 57%. R_f = 0.625 (cyclohexane/EtOAc: 70/30); $[\alpha]_D^{25}$ +69 (c 1.0, CH_2Cl_2); mp. 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.7 Hz, 6H), 1.56 (s, 3H), 1.63 (s, 3H), 2.41−2.48 (m, 1H), 3.65 (d, J = 8.6 Hz, 1H), 3.80 (d, J = 8.6 Hz, 1H), 4.32 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 7.10−7.15 (m, 3H), 7.24−7.31 (m, 4H), 7.37−7.43 (m, 1H), 7.79 (dd, J = 7.1, 4.1 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 1709, 19.3, 23.4, 23.9, 28.2, 61.5, 78.3, 84.6, 87.4, 115.3, 127.8 (2 x CH), 128.2 (2 x CH), 128.4 (2 x CH), 129.1, 129.3 (2 x CH), 132.8, 125.1, 137.8, 157.5, 164.2, 194.7 ppm; IR (neat): υ 1668, 1261, 1176, 730, 712 cm^{-1}; HRMS (EI) m/z: calculated for $C_{25}H_{28}NO_4$ $[M+H]^+$: 406.2018, found: 406.2016.

Procedure To Prepare (S,R)-5aE. A solution of Michael acceptor **1a** (70.1 mg, 0.25 mmol), (*R*)-2-bromo-*N*-(2-hydroxy-1-phenylethyl)-2-methylpropanamide (*R*)-**2E** (85.8 mg, 0.3 mmol, 1.2 equiv) and cesium carbonate (0.25 mmol, 1 equiv) were dissolved in freshly distilled CH_3CN (2 mL). The resulting mixture was stirred for 12 h and was then quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$ and evaporated. The residue was then chromatographed on silica gel to give the desired compound (*S*,*R*)-**5aE**.

(3*R*,9a*S*)-9-Benzoyl-6,6-dimethyl-3,8-diphenyl-6,9a-dihydro-2*H*-oxazolo[3,2-*d*] [1,4]oxazepin-5(3*H*)-one (*S*,*R*)-5aE. The crude material was purified by flash chromatography on silica gel (eluting with cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. 62.6 mg. Yield: 57%. R_f = 0.6 (cyclohexane/EtOAc: 70/30); $[\alpha]_D^{25}$ −3.3 (c 1.0, CH_2Cl_2); mp. 151−153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.69 (s, 3H), 3.88 (dd, J = 8.6, 3.5 Hz, 1H), 4.38 (dd, J = 8.6, 6.5 Hz, 1H), 5.43 (dd, J = 6.4, 3.5 Hz, 1H), 6.82 (s, 1H), 7.22−7.24 (m, 3H), 7.36−7.55 (m, 10H), 7.92 (dd, J = 7.1, 1.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 28.2, 60.1, 72.3, 85.0, 85.5, 126.2 (2 x CH), 126.7 (2 x CH), 127.7, 128.4 (2 x CH), 128.7 (4 x CH), 129.3 (2 x CH), 129.4, 131.9, 133.8, 135.3, 136.7, 140.0, 153.2, 170.8, 193.4 ppm; IR (neat): υ 1725, 1651, 1403, 1075, 670 cm^{-1}; HRMS (EI) m/z: calculated for $C_{28}H_{26}NO_4$ $[M+H]^+$: 440.1832, found 440.1850.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00629.

X-ray crystallographic data for compound **5aB** (CIF)
X-ray crystallographic data for compound **5aD** (CIF)
X-ray crystallographic data for compound (*S*,*R*)-**5aE** (CIF)
DFT calculation details; X-ray diffraction study of **5aB**, **5aD**, and (*S*,*R*)-**5aE**; ^{1}H and ^{13}C spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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