JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

Regioselective Functionalization of Ester-, Amide-, Carbonate-, and Carbamate-Substituted 2-Phenyl-2-oxazolines with Mixed Lithium–Magnesium Amides

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Cite This: https://dx.doi.org/10.1021/acs.joc.0c02369 Read Online

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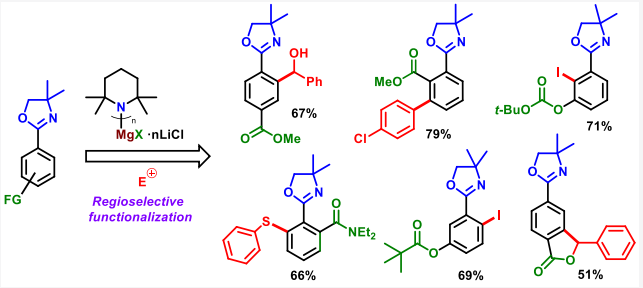
ABSTRACT: We have prepared novel highly functionalized benzene derivatives by regioselective metalation of ester-, amide-, carbamate-, and carbonate-substituted 2-phenyl-2-oxazolines with mixed lithium–magnesium amides followed by reaction with different electrophiles. While a complementary metalation site can be accessed by using different bases, steric and electronic effects promoted by the aromatic ring substituents also play an important role in reaction regioselectivity. Computational calculations of the aromatic hydrogen pK_a values have helped us to rationalize the metalation preference by the complex-induced proximity effect concept.

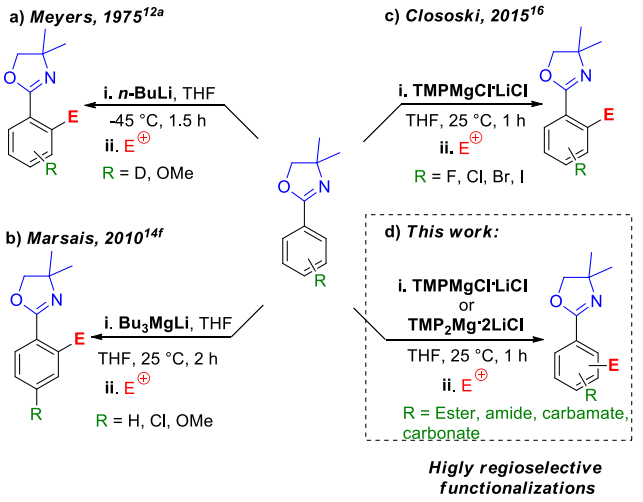


Molecules bearing 2-oxazoline rings display diverse biological activities including antibiotic,[1] anti-inflammatory,[2] antimalarial,[3] anticancer,[4] and antidepressant[5] actions. In addition, the 2-oxazoline function has already proved its synthetic utility as a carboxylic acid protecting group and ligand in asymmetric synthesis,[6−8] being pyridino-bis-2-oxazolines (PYBOX)[7] and bis-oxazolines (BOX)[8] the most frequently used derivatives.

Developing selective protocols to obtain functionalized aromatic compounds is essential in natural product synthesis and drug discovery.[9] Although numerous reactions concerning transition metal-mediated C−H activation of aromatics have been developed,[10] only a few reactions offer more regioselectivity and efficiency than the *ortho*-metalation of aromatics.[11] Initially explored by Meyers and co-workers,[12] the *ortho*-lithiation of 2-aryl-2-oxazolines is a classic strategy in organic synthesis.[12] However, the organolithium intermediates are highly reactive, which is an important drawback that may preclude the presence of sensitive functional groups in the substrate.[13] To address this issue, an interesting approach is to explore the higher tolerance of organomagnesium reagents (Scheme 1).[14]

Over the past decade, the mixed lithium–magnesium amides TMPMgCl·LiCl and $TMP_2Mg·2LiCl$ (TMP = 2,2,6,6-tetramethylpiperidine) have emerged as alternative reagents for the metalation of aromatic and heterocyclic substrates.[15] Given our interest in regioselective metalation reactions and the medicinal importance of the 2-oxazoline core, our research group has reported the selective functionalization of halophenyl-2-oxazolines[16] and cyanophenyl-2-oxazolines[17]

Scheme 1. Some Strategies for the Functionalization of 2-Phenyl-2-oxazolines Using Metalation



Received: October 6, 2020

https://dx.doi.org/10.1021/acs.joc.0c02369
J. Org. Chem. XXXX, XXX, XXX−XXX

with TMPMgCl·LiCl at room temperature. In both cases, the powerful ability of the 2-oxazolinyl group to direct metalation at the *ortho* position overcame the influence of the halogen- and cyano-substituents. Recently, Nachtsheim and co-workers reported the use of an excess of the same base to promote direct hydroxylations of several 2-aryloxazolines.[18]

On the basis of our last results,[16,17] we have envisaged that 2-phenyl-2-oxazolines bearing more hindered and coordinating substituents, such as esters, amides, carbamates, and carbonates, could open different possibilities to explore the regioselective functionalization of the aromatic ring via TMPMgCl·LiCl and $TMP_2Mg·2LiCl$.

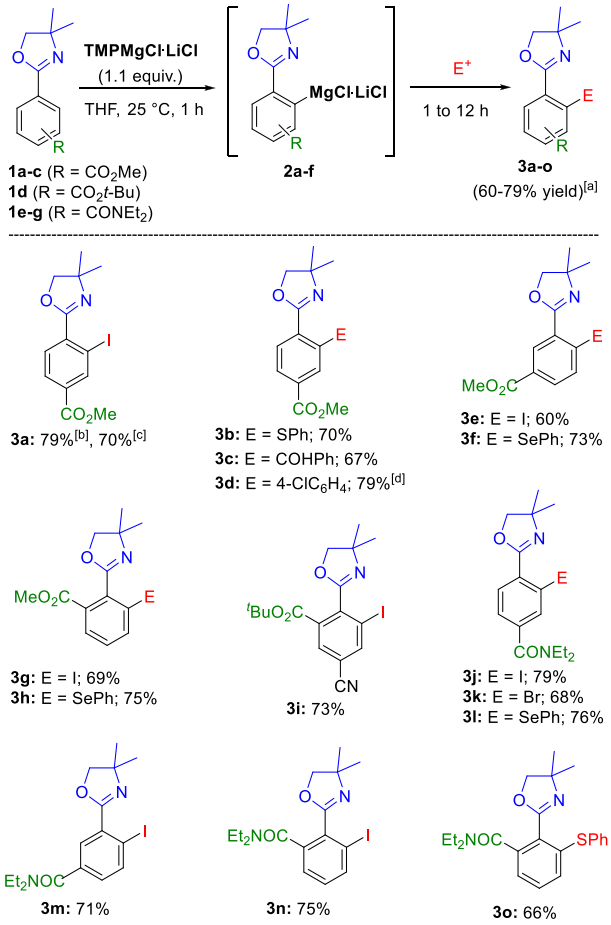
We initiated our study by preparing the 2-phenyl-2-oxazolines bearing methyl ester groups at the *ortho*, *meta*, or *para* position (**1a−c**) from the corresponding substituted benzaldehydes.[19] To determine the best base for the metalation of these substrates, we used **1a** as a model substrate and varied the reaction conditions. We monitored the metalation reactions by analyzing reaction aliquots quenched with iodine by GC−MS. As expected, attempts to perform the lithiation of **1a** with *n*-BuLi or LDA (1.1 equiv, −78 °C, 1 h) exclusively afforded ester group addition products (tertiary alcohol and amide in 50 and 59% isolated yields, respectively). In contrast, while TMPLi and TMPZnCl·LiCl presented low reactivity toward **1a**, the mixed lithium magnesium amide TMPMgCl·LiCl (1.1 equiv) successfully provided complete magnesiation of the starting material at room temperature within one hour. After iodination, we isolated the iodide **3a** in 79% yield (Scheme 2), confirming that magnesiation occurred at the *ortho* position of the 2-oxazoline group.

Quenching the organomagnesium **2a** with diphenyl disulfide and benzaldehyde afforded **3b** and **3c** in 70% and 67% yields, respectively (Scheme 2). The transmetalation of this organomagnesium reagent with $ZnCl_2$ followed by reaction with 1-chloro-4-iodobenzene in the presence of $Pd(PPh_3)_4$ (4 mol %) produced the expected biaryl derivative **3d** in 79% yield.

Interestingly, steric and electronic factors appeared to govern the magnesiation of the phenyl-2-oxazoline **1b** with TMPMgCl.LiCl in the synthesis of **3e** and **3f** in 60 and 73% yields, respectively. Additionally, in the case of the *ortho*-substituted substrate **1c**, the powerful ability of the 2-oxazolinyl group to direct metalation at the *ortho* position also seemed to overcome the influence of the methyl ester substituent, giving the derivatives **3g** and **3h** in 69 and 75% yields after the reaction of **2c** with iodine and diphenyl diselenide, respectively. Notably, this oxazoline *ortho*-directing metalation effect also allowed the regioselective synthesis of the tetrasubstituted derivative **3i** in 73% yield from **1d** bearing the *t*-butyl ester group. Due to its high stability toward organometallic reagents, amides were also considered as substituents of 2-phenyl-2-oxazolines. We prepared compounds **1e−g** and used **1e** as a model substrate in the preliminary metalation studies. Interestingly, when we used 1.1 equiv of TMPMgCl·LiCl, we achieved full, exclusive metalation at the *ortho* position to the 2-oxazoline group within one hour. We obtained six trisubstituted compounds (**3j−o**) with yields ranging from 66 to 79% (Scheme 2).

Contrary to TMPMgCl·LiCl, the metalation of type **1a−c** substrates with $TMP_2Mg·2LiCl$ preferentially occurred at the *ortho* position relative to the ester groups (Scheme 3). Hence, the reaction of **1a** with 1.4 equiv of $TMP_2Mg·2LiCl$ led to complete magnesiation of the starting material within 1 h. Quenching of the organomagnesium **4a** with iodine and

Scheme 2. Selective Metalation of 2-Phenyl-2-oxazolines Bearing Ester or Amide Groups with TMPMgCl·LiCl followed by Reactions with Electrophiles [Substrates: Methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1a), Methyl 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1b), Methyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1c), 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-*N*,*N*-diethylbenzamide (1e), 3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-*N*,*N*-diethylbenzamide (1f), 2-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-*N*,*N*-diethylbenzamide (1g)]



[a]Isolated yields. [b]0.05 mmol scale. [c]10 mmol scale (2.51 g of **3a** was isolated). [d]4 mol % [$Pd(PPh_3)_4$] under Negishi cross-coupling reaction conditions using an oil bath as a heat source after transmetalation with 1 mol L^{-1} $ZnCl_2$ anhydrous solution in THF.

diphenyl diselenide gave the corresponding functionalized derivatives **5a** and **5b** in moderate yields. Furthermore, the reaction of **4a** with benzaldehyde afforded the lactone derivative **5c** in 51% yield. As a limitation, the reaction of **1b** with $TMP_2Mg·2LiCl$ was not selective, giving mixtures of iodides (1:1 ratio of both isomers) after the reaction was quenched with iodine. On the other hand, trapping **4c** with iodine, diphenyl disulfide, and diphenyl diselenide produced **5d**, **5e**, and **5f** with yields up to 69%. Finally, after transmetalation of **4c** with $ZnCl_2$, a Negishi cross-coupling reaction with 1-chloro-4-iodobenzene in the presence of $Pd(PPh_3)_4$ (4 mol %) provided **5g** in 79% yield.

We also studied the metalation of 2-phenyl-2-oxazolines bearing pivalate, carbonate, and carbamate as bulky groups. As

https://dx.doi.org/10.1021/acs.joc.0c02369
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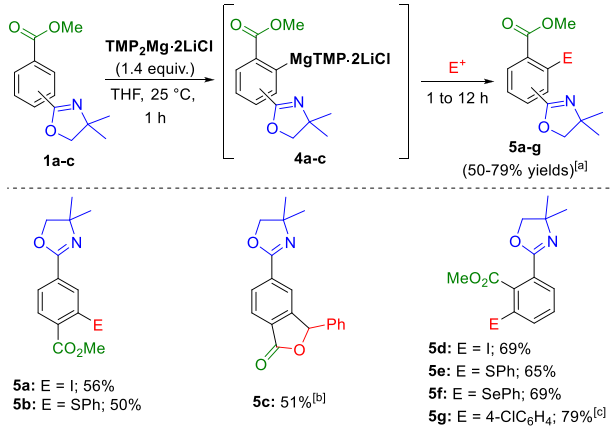
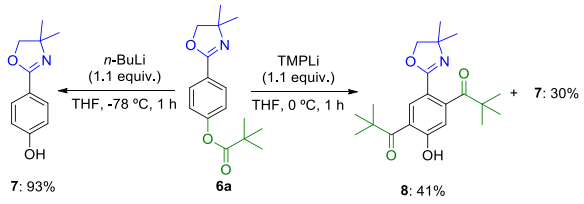
Scheme 3. Selective Metalation of 2-Phenyl-2-oxazolines Bearing an Ester Group with $TMP_2Mg·2LiCl$ followed by Reactions with Electrophiles



[a]Isolated yields. [b]Reaction quenching with benzaldehyde gave the lactone derivative as the only product. [c]Four mol % $[Pd(PPh_3)_4]$ under Negishi cross-coupling reaction conditions using an oil bath as a heat source after transmetalation with 1 mol L^{-1} $ZnCl_2$ anhydrous solution in THF.

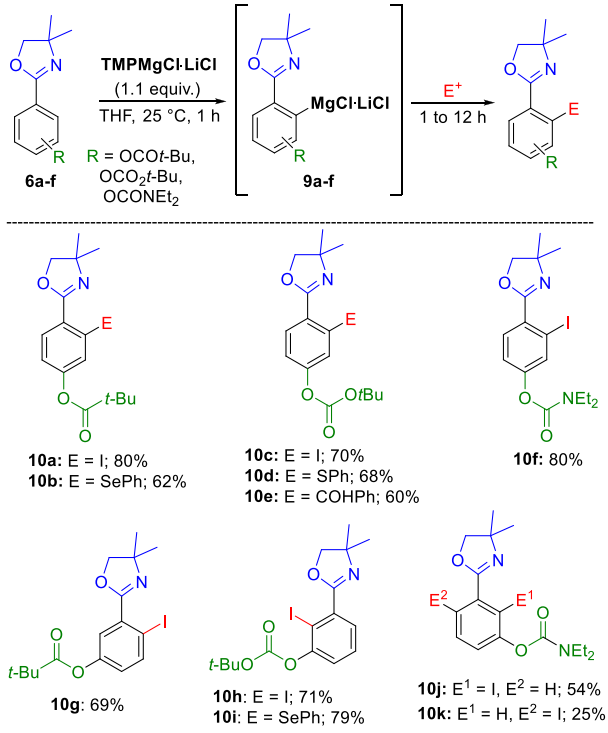
expected, attempts to promote lithiation of **6a** with *n*-BuLi (−78 °C for 1 h) gave the phenol **7** as a result of nucleophilic attack at the ester group. Moreover, the use of the more hindered lithium base TMPLi afforded a mixture of **7** and the diketone **8**. In this case, **8** could arise from an intermolecular attack of the generated *ortho*-2-oxazoline anion to the ester group in the substrate, whereas the respective acylated product, which was even more reactive than the substrate (for pK_a calculations, see Supporting Information), could undergo new deprotonation, to give **8** after an anionic Fries rearrangement (Scheme 4).

Scheme 4. Reaction of 2-Phenyl-2-oxazoline 6a with *n*-BuLi and TMPLi



The bases TMPMgCl·LiCl and $TMP_2Mg·2LiCl$ showed similar reactivity toward **6a**, which allowed iodination at the *ortho* position of the 2-oxazoline group furnishing **10a** in 80% yield. Therefore, we decided to use TMPMgCl·LiCl to synthesize other trisubstituted derivatives of type **10** (Scheme 5). This base also tolerated the presence of the Boc and carbamate groups at the *para* position. Quenching the organomagnesium intermediates **9a−f** with different electrophiles afforded derivatives **10a−f** in 60 to 80% yields. Interestingly, metalation of the substrate bearing Boc and pivaloyl groups at the *meta* position (**6d** and **6e**) appeared to present complementary regioselectivity, producing **10g−i** in good yields. Thus, after magnesiation of **6d** with TMPMgCl·LiCl, further iodination afforded exclusively **10g** in 69% yield. This mixed lithium−magnesium amide also tolerated the

Scheme 5. Magnesiation of 2-Phenyl-2-oxazolines of Type 6 followed by Reactions with Electrophiles



[a]Isolated yields.

presence of the Boc group in **9e**, allowing efficient metalation at the *ortho* position to the 2-oxazoline function at room temperature within 1 h. Quenching the organomagnesium intermediate with iodine or diphenyl diselenide enabled us to isolate the corresponding derivatives **10h** and **10i** in 71 and 79% yields, respectively. In contrast, magnesiation of carbamate **6f** followed by iodination gave a mixture of C-2 and C-4 iodo-substituted isomers **10j** and **10k** in 54 and 25% yields, respectively.

To rationalize the reactivity of the substrates and the regioselective control observed during the metalation of 2-phenyl-2-oxazolines, we conducted a computational study to obtain the pK_a values for the aromatic hydrogens of these compounds. The use of computational chemistry to calculate pK_a values is currently an important tool to guide experimental design.[20]

According to the computational study, in the case of substrates type **1** in THF, the most acidic H atom of the aromatic ring is located at the *ortho* position in relation to the ester or the amide group (pK_a values around 42; see Experimental Section). Furthermore, the most acidic hydrogens in the studied phenyl pivalates (pK_a: 34.9−38.6), phenyl carbonates (pK_a: 38.0−39.4), and carbamates (pK_a: 38.8−41.3) are located at the *ortho* position relative to these functional groups. When the base TMPMgCl·LiCl is used, deprotonation of the carbon in the *ortho* position to the oxazolinyl group is clearly related to the directing metalation effect promoted by the oxazoline group nitrogen and may be rationalized by the complex-induced proximity effect concept affording kinetic rather than the expected thermodynamic products.[21]

DFT calculations have been used to investigate how substrate complexation with metal amides and salts affects

https://dx.doi.org/10.1021/acs.joc.0c02369
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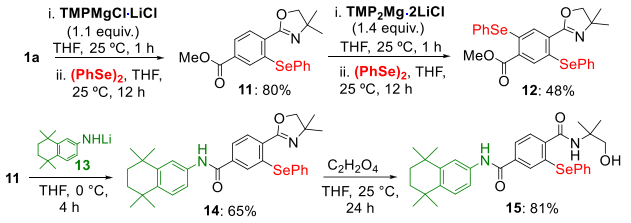
the regioselectivity and deprotonation rates.[22,23] Here, we employed DFT calculations to investigate how oxazoline group coordination with both LiCl and TMPMgCl influenced the acidity of the aromatic hydrogens of substrates **1a–c** (see Experimental Section). While the acidity of the hydrogens that are in the vicinity of the 2-oxazoline group that coordinates to both reagents (LiCl and TMPMgCl) clearly increased, coordination of the substrates with TMPMgCl appeared to generate more stable complexes and to affect the pK_a values more significantly. Moreover, the effect of base coordination on the acidity of H-4 appeared to be crucial to rationalize the selective metalation of *meta*-substituted phenyl-2-oxazolines such as substrate **1b** by TMPMgCl·LiCl. Furthermore, the complementary reactivity of the base $TMP_2Mg{\cdot}2LiCl$ with substrates of type **1** may be associated with faster complexation with the ester or the amide groups present in these molecules, while the different regioselectivity observed in the metalation of 2-oxazoline substrates of type **6** bearing bulky groups provided insights into how a combination of electronic and steric effects governed these reactions.

To illustrate the synthetic relevance of the developed methodologies, we also evaluated the sequential regioselective difunctionalization of a 2-phenyl-2-oxazoline by using the mixed lithium/magnesium base. Thus, after selective magnesiation of **1a** at the *ortho* position to the 2-oxazoline group with TMPMgCl·LiCl, reaction with diphenyl diselenide led to **11** in 80% yield. Subsequently, magnesiation at the *ortho* position to the methyl ester group of **11** with $TMP_2Mg{\cdot}2LiCl$ followed by quenching of the same electrophile afforded the tetrasubstituted aromatic derivative **12** in 48% yield. Moreover, functionalized phenyl-2-oxazoline **11** was used as a substrate to synthesize a derivative of tamibarotene, a synthetic retinoid that is used to treat acute promyelocytic leukemia (APL) in Japan and a potential candidate to treat Alzheimer's disease.[24] Thus, the reaction of **11** with the lithium amide **13**[25] in THF at 0 °C for 4 h furnished **14** in 65% yield. Subsequent hydrolysis in the presence of oxalic acid generated the tamibarotene derivative **15** in 81% yield (Scheme 6).

Scheme 6. Difunctionalization of 1a Using Sequential Regioselective Metalations and Synthesis of the Tamibarotene Derivative 15



We have demonstrated that numerous substituted benzene derivatives can be prepared in a regioselective fashion by using the mixed lithium–magnesium amides TMPMgCl·LiCl and $TMP_2Mg{\cdot}2LiCl$. Interestingly, even when competitive *ortho*-directing groups such as esters, amides, carbamates, and carbonates are attached to the aromatic ring, the metalation of 2-phenyl-2-oxazolines with TMPMgCl·LiCl occurs exclusively at the *ortho* position to the 2-oxazoline group. On the other hand, complementary regioselectivity can be obtained when the methyl ester-substituted 2-phenyl-2-oxazolines are metalated with the diamide $TMP_2Mg{\cdot}2LiCl$. In both cases, the organomagnesium species generated with TMPMgCl·LiCl and $TMP_2Mg{\cdot}2LiCl$ are straightforwardly trapped with distinct electrophiles to afford a series of substituted oxazolines in moderate to high yields. As expected, steric and electronic effects promoted by the aromatic ring substituents also play an important role in the metalation regioselectivity. Moreover, computational calculations of the aromatic hydrogen pK_a values have helped us to rationalize the metalation preference by the complex-induced proximity effect concept. To exemplify the feasibility and the synthetic potential of this chemistry, we have described the prompt preparation of an anticancer tamibarotene derivative.

EXPERIMENTAL SECTION

General Considerations. The solvents were purified according to standard procedures.[26] The starting materials were purchased from Sigma-Aldrich Corp. All air-sensitive and/or water-sensitive reactions were carried out with dry solvents under anhydrous conditions and a nitrogen atmosphere. Standard syringe techniques were applied to transfer dry solvents and air-sensitive reagents. The reactions performed under heating comprised the use of an oil bath. The reactions were monitored by TLC on Merck silica gel (60 F 254) by using UV light. Aldrich silica gel (particle size 0.040–0.063 nm) was used for flash chromatography. The NMR spectra were recorded on Bruker DPX 300, 400, and 500 instruments (at 300, 400, and 500 MHz for protons and at 75, 100, and 125 MHz for carbon-13, respectively). $CDCl_3$, methanol-d_4, and DMSO-d_6 were employed as solvents. The chemical shifts are reported as δ units in parts per million (ppm) relative to the solvent residual peak as the internal reference. Coupling constants (J) are reported in hertz, and multiplicities of NMR signals are abbreviated as follows: bs = broad singlet, s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, td = triplet of doublets, m = multiplet, q = quartet and combinations thereof, app = apparent. The melting point values (mp) were determined in a Büchi brand, model B-545. The HRMS spectra were acquired on a Bruker Daltonics micrOTOF QII/ESI-TOF.

*Typical Procedure 1 (TP1): General Procedure for the Preparation of Ester-, Carbonate and Carbamate-Substituted 2-Phenyl-2-Oxazolines (**1a–d** and **6a–f**).* 2-Amino-2-methyl-1-propanol (0.9 mL, 1.8 g, 10 mmol) was dissolved in CH_2Cl_2 (60 mL), and the substituted benzaldehyde (10 mmol) was added. The mixture was stirred over molecular sieves (4 Å, 10 g) for 14 h. Afterward, *N*-bromosuccinimide (1.8 g, 10 mmol) was added, and the solution was stirred for 30 min. The mixture was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ solution (100 mL) and H_2O (30 mL). The organic layer was dried with $MgSO_4$, and the solvent was removed under pressure. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

*Typical Procedure 2 (TP2): General procedure for the preparation of amide-substituted 2-phenyl-2-oxazolines (**1e–g**).* In a flame-dried flask flushed with nitrogen and equipped with a magnetic stirring bar, diethylamine (0.57 mL, 5.5 mmol) was dissolved in THF (10 mL). This solution was cooled to −78 °C, and *n*-BuLi solution (2.3 M in hexane, 2.13 mL, 5.0 mmol) was added dropwise. After the addition was completed, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. The corresponding methyl ester-substituted 2-phenyl-2-oxazoline (**1a–c**) (1.16 g, 5.0 mmol) was dissolved in THF (10 mL) and added to the reaction mixture at 0 °C, and the mixture was stirred for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL), extracted with ethyl acetate (3 × 50 mL), and dried with $MgSO_4$. After filtration, the solvent was removed under a vacuum. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

Typical Procedure 3 (TP3): Preparation of TMPMgCl·LiCl in THF. A dry and nitrogen-flushed Schlenk flask equipped with a magnetic stirring bar and rubber septum was charged with *i*-PrMgCl·LiCl (1.0

https://dx.doi.org/10.1021/acs.joc.0c02369
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mol/L in THF, 20 mL, 20 mmol). Then, 2,2,6,6-tetramethylpiperidine (3.52 mL, 21 mmol) was added dropwise through a syringe within 5 min. The mixture was stirred until gas evolution ceased (48 h). Titration against benzoic acid in THF (0 °C) in the presence of 4-(phenylazo)diphenylamine as the indicator showed that the base concentration ranged from 0.90 to 0.98 M.

Typical Procedure 4 (TP4): Selective Magnesiation of 2-Phenyl-2-oxazolines with TMPMgCl·LiCl followed by Reaction with Electrophiles. In a dry nitrogen-flushed round-bottom flask under magnetic stirring containing 2 mL of THF and the 2-phenyl-2-oxazoline (0.50 mmol), a TMPMgCl·LiCl solution (0.9 M, 0.62 mL, 0.55 mmol) was added dropwise at 25 °C. After stirring for 1 h, a solution of an appropriate electrophile (1.3 equiv) in THF (1.0 mL) was added, and the reaction mixture was kept under stirring from 1 h (iodine) to 12 h (other electrophiles). The reaction was quenched with saturated aqueous $Na_2S_2O_4$ (iodine) or NH_4Cl (other electrophiles), the products were extracted with ethyl acetate (3 × 15 mL), and the organic layer was dried with $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

Typical Procedure 5 (TP5): Preparation of TMP_2Mg·2LiCl. In a dry 25 mL flask under a nitrogen atmosphere and equipped with magnetic stirring, 2,2,6,6-tetramethylpiperidine (0.12 mL, 0.725 mmol) was dissolved in THF (2 mL). The solution was cooled to −78 °C, and *n*-BuLi (2.35 M, 0.3 mL, 0.7 mmol) was added dropwise. After that, the reaction mixture was warmed to 0 °C and was left at this temperature for 30 min. Previously titrated TMPMgCl·LiCl (0.9 M, 0.78 mL, 0.7 mmol) was then added dropwise to the reaction mixture, which was left at 0 °C for 15 min and at room temperature for 30 min.

Typical Procedure 6 (TP6): Selective Magnesiation of 2-Phenyl-2-oxazolines with TMP_2Mg·2LiCl followed by Reaction with Electrophiles. Following TP5, phenyl-2-oxazoline was added (116.0 mg, 0.5 mmol) in THF (2.0 mL). After stirring for 1 h, a solution of an appropriate electrophile (1.3 equiv) in THF (1.0 mL) was added, and the reaction mixture was kept under stirring for 1 h (for iodine) to 12 h (other electrophiles). The reaction was quenched with saturated aqueous NH_4Cl, the products were extracted with ethyl acetate (3 × 15 mL), and the organic layer was dried with $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

*Methyl 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**).* Following TP1, methyl 4-formylbenzoate (1.64 mg, 10 mmol) afforded **1a** (1.86 g, 80%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 68−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d-like, 2H), 8.01 (d-like, 2H), 4.14 (s, 2H), 3.94 (s, 3H), 1.40 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5, 161.3, 132.3, 132.1, 129.5 (2C), 128.2 (2C), 79.3, 67.9, 52.2, 28.2 (2C); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{15}NNaO_3$ 256.0944, found 256.0965.

*Methyl 3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1b**).* Following TP1, methyl 3-formylbenzoate (1.64 mg, 10 mmol) afforded **1b** (1.63 g, 70%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 54−57 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59−8.59 (m, 1H), 8.15−8.13 (m, 2H), 7.49 (t, J = 8.8 Hz, 1H), 4.14 (s, 2H), 3.93 (s, 3H), 1.40 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.4, 161.2, 132.4, 132.1, 130.4, 129.3, 128.5, 128.4, 79.2, 67.7, 52.1, 28.3 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{16}NO_3$ 234.1125, found 234.1125.

*Methyl 2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1c**).* Following TP1, methyl 2-formylbenzoate (1.64 mg, 10 mmol) afforded **1c** (1.81 g, 82%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−7.71 (m, 2H), 7.52−7.45 (m, 2H), 4.09 (s, 2H), 3.86 (s, 3H), 1.38 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.0, 162.1, 131.9, 131.0, 130.3, 129.7, 129.0, 128.5, 79.8, 67.8, 52.3, 28.1 (2C); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{15}NNaO_3$ 256.0944, found 256.0948.

*tert-Butyl 5-Cyano-2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-benzoate (**1d**).* Following TP4, 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzonitrile (600 mg, 3 mmol) and di-*tert*-butyl decarbonate (0.9 mL, 3.9 mmol) afforded **1d** (540 mg, 60%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 121−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 1.5 Hz, 1H), 7.84, (d, J = 8.1 Hz, 1H), 7.71 (dd, J = 8.1, 1.5 Hz, 1H), 4.16 (s, 2H), 1.51 (s, 9H), 1.40 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.4 (2C), 137.2, 135.2, 133.7, 132.5, 130.8, 117.3, 114.9, 83.5, 80.7, 67.8, 28.0 (3C), 27.7 (2C); HRMS (ESI) m/z [M + H]$^+$calcd for $C_{17}H_{21}N_2O_3$ 301.1547, found 301.1543.

*4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-N,N-diethylbenzamide (**1e**).* Following TP2, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**, 1.16 g, 5.0 mmol) afforded **1e** (1.10 g, 80%) as a white solid after chromatographic purification with hexanes/ethyl acetate (7:3−100% ethyl acetate) as an eluent: mp 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d-like, J = 8.6 Hz, 2H), 7.40 (d-like, J = 8.6 Hz, 2H), 4.12 (s, 2H), 3.56−3.54 (m, 2H), 3.22−3.21 (m, 2H), 1.39 (s, 6H), 1.27−1.23 (m, 3H), 1.11−1.08 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 161.5, 139.8, 128.7, 128.3 (2C), 126.2 (2C), 79.2, 67.7, 43.2, 39.3, 28.4 (2C), 14.1, 12.8; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_2$ 275.1754, found 275.1766.

*3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-N,N-diethylbenzamide (**1f**).* Following TP2, methyl 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1b**, 1.16 g, 5.0 mmol) afforded **1f** (1.25 g, 91%) as a colorless oil after chromatographic purification with hexanes/ethyl acetate (7:3−100% ethyl acetate) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.95 (m, 2H), 7.48−7.42 (m, 2H), 4.12 (s, 2H), 3.55−3.54 (m, 2 H), 3.25−3.24 (m, 2 H), 1.38 (s, 6H), 1.26−1.24 (m, 3 H), 1.10 (bs, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.2, 161.3, 137.3, 128.7, 128.6, 128.3, 128.2, 126.0, 79.1, 67.5, 43.2, 39.2, 28.2 (2C), 14.0, 12.7; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_2$ 275.1754, found 275.1755.

*2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-N,N-diethylbenzamide (**1g**).* Following TP2, methyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1c**, 1.16 g, 5.0 mmol) afforded **1g** (1.25 g, 91%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (7:3−100% ethyl acetate) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.95 (m, 1H), 7.47 (td, J = 7.3, 1.3 Hz, 1H), 7.39 (td, J = 7.3, 1.3 Hz, 1H), 7.28−7.25 (m, 1H), 4.04 (s, 2H), 3.84−3.28 (m, 2H), 3.10 (q, J = 7.3 Hz, 2H), 1.34 (s, 6H), 1.25 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.1, 161.0, 137.6, 130.9, 129.6, 128.2, 126.7, 124.7, 79.0, 67.7, 42.5, 38.6, 28.2 (2C), 13.4, 11.9; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_2$ 275.1754, found 275.1754.

*Methyl 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-iodobenzoate (**3a**).* Following TP4, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**, 116 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **3a** (141.8 mg, 79%) as a white solid after chromatographic purification with hexane/ethyl acetate (8:2) as an eluent. For the scale-up procedure, following TP4, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**, 2.33 g, 10 mmol) and iodine (3.30 g, 13 mmol) afforded **3a** (2.51 g, 70%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 70−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.3 Hz, 1H), 8.02 (dd, J = 8.1, 1.4 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 4.17 (s, 2H), 3.93 (s, 3H), 1.43 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.9, 162.0, 141.0, 138.1, 132.6, 130.3, 128.7, 94.2, 79.5, 68.4, 52.5, 28.1 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{15}INO_3$ 360.0091, found 360.0091.

*Methyl 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-(phenylthio)-benzoate (**3b**).* Following TP4, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**, 116 mg, 0.5 mmol) and diphenyl disulfide (141 mg, 0.65 mmol) afforded **3b** (119.3 mg, 70%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: mp 112−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 1H), 7.77 (dd, J = 8.0, 1.5 Hz, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.53−7.50 (m, 2H), 7.43−7.38 (m, 3H), 4.11 (s, 2H), 3.80 (s, 3H), 1.42 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz,

https://dx.doi.org/10.1021/acs.joc.0c02369
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$CDCl_3$) δ 166.0, 160.6, 140.7, 134.3 (2C), 132.9, 132.0, 130.1, 130.1, 129.7 (2C), 129.3, 128.8, 125.6, 79.0, 68.7, 52.2, 28.4 (2C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{20}NO_3S$ 342.1158, found 342.1158.

*Methyl 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-(hydroxy-(phenyl)methyl)benzoate (**3c**).* Following TP4, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**, 116 mg, 0.5 mmol) and benzaldehyde (0,07 mL, 0.65 mmol) afforded **3c** (113.5 mg, 67%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 109−111 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.1, 1.7 Hz, 1H), 7.95−7.93 (m, 2H), 7.81 (d, J = 8.5 Hz, 1H), 7.26−7.24 (m, 5H), 5.98 (d, J = 8.5 Hz, 1H), 4.03 (d, J = 8.1 Hz, 1H), 3.93 (d, J = 8.1 Hz, 1H), 3.91 (s, 3H), 1.34 (s, 3H), 0.96 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 161.5, 144.6, 142.8, 132.1, 131.2, 130.6 (2C), 128.4, 127.6 (2C), 126.5, 126.2 (2C), 78.7, 74.9, 67.9, 52.1, 27.9, 27.4; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{22}NO_4$ 340.1543, found 340.1553.

*Methyl 4′-Chloro-6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-[1,1′-biphenyl]-3-carboxylate (**3d**).* Following TP4, a $ZnCl_2$ solution in THF (1 mol/L in THF, 0.5 mL, 0.5 mmol) was added after complete metalation of methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-benzoate (**1a**, 116 mg, 0.5 mmol). After 15 min, a $Pd(PPh_3)_4$ solution (4 mol %) in THF (1 mL) and a 1-chloro-4-iodobenzene (155.0 mg, 1.3 mmol) solution in THF (1 mL) were added, and the resulting mixture was stirred at 60 °C overnight. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the aqueous layer was extracted with EtOAc (3 × 15 mL). The solvent of the combined organic layers was evaporated under a vacuum, to afford **3d** (135.4 mg, 79%) as a brown solid after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: mp 132−135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05−8.03 (m, 2H), 7.82 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 3.94 (s, 3H), 3.85 (s, 2H), 1.30 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 162.5, 140.6, 138.6, 133.7, 132.0, 131.9, 131.1, 130.4, 129.6 (2C), 128.2, 128.2 (2C), 79.5, 67.8, 52.3, 27.9 (2C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{19}ClNO_3$ 344.1048, found 344.1046.

*Methyl 3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-4-iodobenzoate (**3e**).* Following TP4, methyl 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1b**, 116 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **3e** (107.7 mg, 60%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 70−72 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 2.3 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.73 (dd, J = 8.3, 2.3 Hz, 1H), 4.17 (s, 2H), 3.92 (s, 3H), 1.44 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 162.0, 140.6, 134.7, 131.8, 131.2, 130.0, 101.1, 79.6, 68.4, 52.4, 28.2 (2C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{15}INO_3$ 360.0091, found 360.0095.

*Methyl 3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-4-(phenylselanyl)benzoate (**3f**).* Following TP4, methyl 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1b**, 116 mg, 0.5 mmol) and diphenyl diselenide (202 mg, 0.65 mmol) afforded **3f** (141.9 mg, 73%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: mp 116−120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.6, 2.0 Hz, 1H), 7.71−7.68 (m, 2H), 7.46−7.40 (m, 3H), 6.95 (d, J = 8.6 Hz, 1H), 4.14 (s, 2H), 3.88 (s, 3H), 1.47 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 160.6, 145.5, 137.2 (2C), 130.9, 130.6, 129.8 (2C), 129.7, 129.2, 128.9, 126.7, 125.9, 78.8, 68.9, 52.1, 28.7 (2C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{20}NO_3Se$ 390.0603, found 390.0603.

*Methyl 2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-iodobenzoate (**3g**).* Following TP4, methyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1c**, 116 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **3g** (123.8 mg, 69%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 73−75 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.8, 1.0 Hz, 1H), 7.89 (dd, J = 7.8, 1.0 Hz, 1H), 7.14 (t, J = 7,8 Hz, 1H), 4.08 (s, 2H), 3.92 (s, 3H), 1.34 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.0, 162.2, 142.8, 135.7, 131.8, 130.7, 129.8, 98.0, 80.0, 68.2, 52.5, 27.7 (2C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{15}INO_3$ 360.0091, found 360.0094.

*Methyl 2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-(phenylselanyl)benzoate (**3h**).* Following TP4, methyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1c**, 116 mg, 0.5 mmol) and diphenyl diselenide (2.02 mg, 0.65 mmol) afforded **3h** (145.8 mg, 75%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: mp 115−118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 7.3, 1.5 Hz, 1H), 7.61−7.59 (m, 2H), 7.36−7.30 (m, 3H), 7.25 (dd, J = 8.0, 1.5 Hz, 1H), 7.21 (t, J = 7.8, 1H), 4.17 (s, 2H), 3.88 (s, 3H), 1.47 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 161.0, 136.0, 135.4 (2C), 134.6, 131.5, 130.2, 129.8, 129.6, 129.5 (2C), 128.4, 127.8, 79.6, 68.5, 52.3, 28.0 (2C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{20}NO_3Se$ 390.0603, found 390.0601.

*tert-Butyl 5-Cyano-2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-3-iodobenzoate (**3i**).* Following TP4, *tert*-butyl 5-cyano-2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1d**, 150 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **3i** (155.5 mg, 73%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (7:3) as an eluent: mp 160−163 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 1.5 Hz, 1H), 8.01 (d, J = 1.5 Hz, 1H), 4.20 (s, 2H), 1.50 (s, 9H), 1.39 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 144.4, 142.7, 135.2, 132.5, 115.9, 114.9, 97.8, 83.7, 80.4, 77.4, 68.4, 28.0 (3C), 27.5 (2C); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{20}IN_2O_3[M + H]^+$ 427.0513, found 427.0551.

*4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-N,N-diethyl-3-iodobenzamide (**3j**).* Following TP4, 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-*N*,*N*-diethylbenzamide (**1e**, 137 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **3j** (158.0 mg, 79%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (1:1−100% ethyl acetate) as an eluent: mp 61−6 4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.37 (dd, J = 7.8, 1.5 Hz, 1H), 4.16 (s, 2H), 3.53−3.52 (m, 2H), 3.20−3.18 (m, 2H), 1.43 (s, 6H), 1.26−1.23 (m, 3H), 1.10−1.07 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 162.2, 140.2, 137.8, 134.8, 130.5, 125.5, 94.7, 79.5, 68.3, 43.2, 39.4, 28.2 (2C), 14.1, 12.8; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{22}IN_2O_2$401.0720, found 401.0721.

*3-Bromo-4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-N,N-diethylbenzamide (**3k**).* Following TP4, 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-*N*,*N*-diethylbenzamide (**1e**, 137 mg, 0.5 mmol) and 1,2-dibromotetrachloroethane (211 mg, 0.65 mmol) afforded **3k** (119.7 mg, 68%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (1:1) as an eluent: ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 1.5 Hz, 1H), 7.34 (dd, J = 7.8, 1.5 Hz, 1H), 4.15 (s, 2H), 3.54−3.52 (m, 2H), 3.21−3.19 (m, 2H), 1.42 (s, 6H), 1.26−1.22 (m, 3H), 1.10−1.07 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 161.0, 140.2, 131.2, 131.1, 130.7, 124.7, 121.8, 79.3, 68.0, 43.1, 39.3, 28.0 (2C), 14.0, 12.7; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{22}BrN_2O_2$ 353.0859, found 353.0860.

*4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-N,N-diethyl-3-(phenylselanyl)benzamide (**3l**).* Following TP4, 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-*N*,*N*-diethylbenzamide (**1e**, 137 mg, 0.5 mmol) and diphenyl diselenide (202 mg, 0.65 mmol) afforded **3l** (152.6, 76%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (1:1) as an eluent: mp 110−113 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 1H), 7.69−7.67 (m, 2H), 7.42−7.35 (m, 3H), 7.17 (dd, J = 8.1, 1.5 Hz, 1H), 6.84 (d, J = 1.5 Hz, 1H), 4.12 (s, 2H), 3.40−3.38 (m, 2H), 3.02−3.00 (m, 2H), 1.46 (s, 6H), 1.12−1.10 (m, 3H), 0.83−0.81 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0, 160.8, 139.1, 138.4, 137.2 (2C), 129.9, 129.7 (2C), 129.6, 129.0, 126.5, 126.3, 123.1, 78.8, 68.7, 42.9, 39.0, 28.6 (2C), 13.9, 12.6; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}N_2O_2Se$ 431.1232, found 431.1232.

*3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-N,N-diethyl-3-iodobenzamide (**3m**).* Following TP4, 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-*N*,*N*-diethylbenzamide (**1f**, 137 mg, 0.5 mmol) and iodine (165

https://dx.doi.org/10.1021/acs.joc.0c02369
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mg, 0.65 mmol) afforded **3m** (120.0 mg, 71%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (1:1−3:7) as an eluent: mp 110−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.11 (dd, J = 8.1, 2.0 Hz, 1H), 4.14 (s, 2H), 3.53−3.52 (m, 2H), 3.24−3.23 (m, 2H), 1.42 (s, 6H), 1.26−1.22 (m, 3H), 1.12−1.10 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 162.1, 140.2, 136.9, 134.4, 129.0, 128.5, 95.5, 79.5, 68.3, 43.3, 39.4, 28.1 (2C), 14.1, 12.7; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{22}IN_2O_2$ 401.0720, found 401.0721.

*2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-N,N-diethyl-3-iodobenzamide (**3n**).* Following TP4, 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-*N*,*N*-diethylbenzamide and iodine (**1g**, 165 mg, 0.65 mmol) afforded **3n** (150.0 mg, 75%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (1:1−3:7) as an eluent: mp 55−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 1H), 7.27 (dd, J = 8.1, 1.3 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 4.11 (s, 2H), 3.51−3.49 (m, 2H), 3.20 (q, J = 7.1 Hz, 2H), 1.39 (s, 6H), 1.23 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 161.6, 139.5, 139.0, 132.3, 130.7, 125.5, 96.8, 79.4, 68.3, 43.3, 39.0, 27.9 (2C), 13.7, 12.8; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{22}IN_2O_2$ 401.0720, found 401.0719.

*2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-N,N-diethyl-3-(phenylthio)benzamide (**3o**).* Following TP4, 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-*N*,*N*-diethylbenzamide and diphenyl disulfide (**1g**, 141 mg, 0.65 mmol) afforded **3o** (126.1 mg, 66%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (1:1) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.48 (m, 2H), 7.40−7.35 (m, 3H), 7.21 (t, J = 7.8 Hz, 1H), 7.06 (dd, J = 7.5, 1.0 Hz, 1H), 6.96 (dd, J = 7.5, 1.0 Hz, 1H), 4.06 (s, 2H), 3.53−3.52 (m, 2H), 3.21 (q, J = 6.9 Hz, 2H), 1.40 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.0, 159.7, 139.9, 138.3, 133.8 (2C), 133.6, 129.9, 129.4 (2C), 129.1, 128.2, 125.5, 123.3, 79.0, 68.4, 43.1, 38.8, 28.0 (2C), 13.6, 12.6; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{27}N_2O_2S$ 383.1788, found 383.1788.

*Methyl 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-iodobenzoate (**5a**).* Following TP6, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**, 116 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **5a** (105.5 mg, 56%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: mp 68−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.5 Hz, 1H), 7.95 (dd, J = 8.1, 1.5 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 4.13 (s, 2H), 3.95 (s, 3H), 1.39 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5, 159.9, 140.7, 137.3, 131.9, 130.5, 127.5, 93.5, 79.4, 68.0, 52.6, 28.3 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{15}INO_3$ 360.0091, found 360.0112.

*Methyl 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-(phenylthio)-benzoate (**5b**).* Following TP6, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**, 116 mg, 0.5 mmol) and diphenyl disulfide (141 mg, 0.65 mmol) afforded **5b** (85.3 mg, 50%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: mp 127−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 1H), 7.76 (dd, J = 8.1, 1.8 Hz, 1H), 7.56−7.53 (m, 2H), 7.44−7.42 (m, 3H), 7.41 (d, J = 1.5 Hz, 1H), 3.97 (s, 2H), 3.95 (s, 3H), 1.30 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5, 160.9, 142.7, 134.8 (2C), 132.4, 131.6, 130.8, 129.7 (2C), 129.4, 129.0, 127.6, 124.5, 79.2, 67.7, 52.3, 28.2 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{20}NO_3S$ 342.1158, found 342.1157.

*5-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-phenylisobenzofuran-1(3H)-one (**5c**).* Following TP6, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**, 116 mg, 0.5 mmol) and benzaldehyde (0.07 mL, 0.65 mmol) afforded **5c** (148.6 mg, 51%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 1H), 7.93−7.89 (m, 2H), 7.32−7.30 (m, 3H), 7.22−7,20 (m, 2H), 6.35 (s, 1H), 4.09 (s, 2H), 1.32 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.7, 161.3, 149.7, 135.8, 133.2, 129.6, 129.4, 129.0 (2C), 127.9, 127.0 (2C), 125.6, 122.9, 82.8, 79.7, 67.8, 28.2 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{18}NO_3$308.1281, found 308.1271.

*Methyl 2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-6-iodobenzoate (**5d**).* Following TP6, methyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1c**, 116 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **5d** (123.8 mg, 69%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 73−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.1, 1.3 Hz, 1H), 7.89 (dd, J = 8.1, 1.3 Hz, 1H), 7.13 (t, J = 8.1 Hz, 1H), 4.07 (s, 2H), 3.92 (s, 3H), 1.34 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.6, 159.4, 141.4, 139.8, 130.2, 128.7, 127.1, 92.8, 79.5, 68.1, 52.6, 28.1 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{15}INO_3$ 360.0091, found 360.0092.

*Methyl 2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-6-(phenylthio)-benzoate (**5e**).* Following TP6, methyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1c**, 116 mg, 0.5 mmol) and diphenyl disulfide (141 mg, 0.65 mmol) afforded **5e** (110.8 mg, 65%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 7.1, 1.5 Hz, 1H), 7.15−7.04 (m, 7H), 3.95 (s, 2H), 3.76 (s, 3H), 1.31 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.9, 160.2, 136.2, 135.0, 135.0, 134.5, 131.6 (2C), 129.6, 129.2 (2C), 128.2, 127.5, 126.6, 79.5, 68.1, 52.3, 28.1 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{20}NO_3S$ 342.1158, found 342.1163.

*Methyl 2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-6-(phenylselanyl)benzoate (**5f**).* Following TP6, methyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1c**, 116 mg, 0.5 mmol) and diphenyl diselenide (202 mg, 0.65 mmol) afforded **5f** (134.2 mg, 69%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.8 Hz, 1H), 7.54−7.52 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.31−7.22 (m, 4H), 4.08 (s, 2H), 3.90 (s, 3H), 1.36 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.0, 160.4, 135.6, 135.5, 134.1 (2C), 131.1, 130.0, 129.6, 129.2 (2C), 127.9, 127.8, 126.9, 79.4, 67.8, 52.2, 27.9 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{20}NO_3Se$ 390.0603, found 390.0624.

*Methyl 4′-Chloro-3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-[1,1′-biphenyl]-2-carboxylate (**5g**).* Following TP6, a $ZnCl_2$ solution in THF was added after complete metalation of methyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1c**, 116 mg, 0.5 mmol) (1 mol/L in THF, 0.5 mL, 0.5 mmol). After 15 min, a $Pd(PPh_3)_4$ solution (4 mol %) in THF (1 mL) and a 1-chloro-4-iodobenzene (155.0 mg, 1.3 mmol) solution in THF (1 mL) were added, and the resulting mixture was stirred at 60 °C overnight. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the aqueous layer was extracted with EtOAc (3 × 15 mL). The solvent of the combined organic layers was evaporated under a vacuum to afford **5g** (135.4 mg, 79%) as a brown solid after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: mp 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.8, 1.3 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.41 (dd, J = 7.8, 1.3 Hz, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 4.08 (s, 2H), 3.66 (s, 3H), 1.36 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.6, 160.5, 139.0, 138.0, 133.8, 133.2, 132.2, 129.8 (2C), 129.1, 128.3 (3C), 126.1, 79.4, 68.0, 52.0, 28.0 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{19}ClNO_3$ 344.1048, found 344.1042.

*4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl Pivalate (**6a**).* Following TP1, 4-formylphenyl pivalate (2.06 g, 10 mmol) afforded **6a** (2.2 g, 81%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 103−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d-like, J = 8.8 Hz, 2H), 7.10 (d-like, J = 8.8 Hz, 2H), 4.10 (s, 2H), 1.38 (s, 6H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.6, 161.4, 153.4, 129.5 (2C), 125.5, 121.4 (2C), 79.2, 67.6, 39.1, 28.4 (2C), 27.1 (3C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{22}NO_3$ 276.1594, found 276.1597.

*tert-Butyl (4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl) Carbonate (**6b**).* Following TP1, *tert*-butyl (4-formylphenyl) carbonate (2.22 g, 10 mmol) afforded **6b** (2.09 g, 76%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as

https://dx.doi.org/10.1021/acs.joc.0c02369
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eluent; 84−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d-like, J = 9.1 Hz, 2H), 6.99 (d-like, J = 9.1 Hz, 2H), 3.97 (s, 2H), 1.51 (s, 9H), 1.33 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3, 153.3, 151.2, 129.5 (2C), 125.5, 121.0 (2C), 83.8, 79.2, 67.6, 28.3 (2C), 27.6 (3C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{22}NO_4$ 292.1543, found 292.1543.

*4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl Diethylcarbamate (**6c**).* Following TP1, 4-formylphenyl 2-ethylbutanoate (2.20 g, 10 mmol) afforded **6c** (2.46 g, 85%) as a white solid after chromatographic purification with hexanes/ethyl acetate (6:4) as an eluent: mp 72−75 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d-like, J = 8.6 Hz, 2H), 7.21 (d-like, J = 8.6 Hz, 2H), 4.10 (s, 2H), 3.40−3.39 (m, 2H), 3.31−3.29 (m, 2H), 1.28 (s, 6H), 1.19 (t, J = 6.8 Hz, 3H), 1.11 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 160.0, 153.6, 152.8, 129.0 (2C), 124.5, 122.0 (2C), 78.5, 67.5, 41.8, 41.6, 28.3 (2C), 14.2, 13.3; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{23}N_2O_3$ 291.1703, found 291.1696.

*3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl Pivalate (**6d**).* Following TP1, 3-formylphenyl pivalate (2.06 g, 10 mmol) afforded **6d** (2.15g, 74%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 50−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (ddd, J = 7.8, 1.5, 1.0 Hz, 1H), 7.66−7.65 (m, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.17 (dq, J = 7.8, 1.0 Hz, 1H), 4.11 (s, 2H), 1.38 (s, 6H), 1.35 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.0, 161.6, 151.3, 129.7, 129.5, 125.7, 124.7, 121.8, 79.5, 67.9, 39.3, 28.6 (2C), 27.4 (3C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{22}NO_3$ 276.1594, found 276.1594.

*tert-Butyl (3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl) Carbonate (**6e**).* Following TP1, *tert*-butyl (3-formylphenyl) carbonate (2.22 g, 10 mmol) afforded **6e** (2.04 g, 70%) as a white solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 52−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (ddd, J = 7.6, 1.0, 1.02 Hz, 1H), 7.76−7.75 (m, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.27−7.25 (m, 1H), 4.11 (s, 2H), 1.56 (s, 9H), 1.38 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2, 151.7, 150.9, 129.6, 129.3, 125.6, 124.1, 121.3, 83.7, 79.2, 67.7, 28.4 (2C), 27.7 (3C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{22}NO_4$ 292.1543, found 292.1548.

*3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl Diethylcarbamate (**6f**).* Following TP1, 4-formylphenyl 2-ethylbutanoate (2.20 g, 10 mmol) afforded **6f** (2.25 g, 78%) as a white solid after chromatographic purification with hexanes/ethyl acetate (6:4) as an eluent: mp 72−75 °C; mp 66−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.79 (m, 1H), 7.70 (bs, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.24−7.22 (m, 1H), 4.12 (s, 2H), 3.39−3.28 (m, 4H), 1.36 (s, 6H), 1.20−1.11 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.8, 151.4, 129.3, 125.6, 125.3, 122.0, 99.9, 79.7, 67.1, 57.3, 42.3, 41.9, 28.1 (2C), 14.2, 13.3; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{23}N_2O_3$ 291.1703, found 291.1688.

*Synthesis of 1,1′-(2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-5-hydroxy-1,4-phenylene)bis(2,2-dimethylpropan-1-one) (**8**).* In a dry 25 mL flask under a nitrogen atmosphere and equipped with magnetic stirring, 2,2,6,6-tetramethylpiperidine (0.10 mL, 0.575 mmol, 1.15 equiv) was dissolved in THF (2 mL). The solution was cooled to −78 °C, and *n*-BuLi (2.35 M, 0.23 mL, 0.55 mmol, 1.1 equiv) was added dropwise. After that, the reaction mixture was warmed to 0 °C and left at this temperature for 30 min. Then, the temperature was lowered to −78 °C, and the 2-oxazoline **6a** (116.0 mg, 0.5 mmol) in THF (3.0 mL) was added. The reaction was stirred at −78 °C for 1 h. Next, saturated aqueous NH_4Cl solution (5 mL) was added. The solution was extracted with ethyl acetate (3 × 20 mL). The resulting organic phase was dried with $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by flash column chromatography with hexanes/ethyl acetate as an eluent (9:1) to give **8** in the form of a yellow solid (73.6 mg, 41%): mp 145−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.01 (s, 1H), 8.59 (s, 1H), 6.67 (s, 1H), 4.04 (s, 2H), 1.48 (s, 9H), 1.31 (s, 6H), 1.27 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 212.6, 211.8, 165.2, 159.0, 149.1, 132.4, 116.4, 116.2, 114.7, 79.2, 68.3, 44.8, 44.7, 28.7 (3C), 28.3 (2), 27.3 (3C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{30}NO_4$ 360.2169, found 360.2168. The phenol derivative **7** (4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenol) was also isolated in the form of a white solid (28,7 mg, 30%): ^{1}H NMR (400 MHz, methanol-d_4) δ 7.74 (d-like, J = 8.8 Hz, 2H), 6.81 (d-like, J = 8.8 Hz, 2H), 4.91 (s, 1H), 4.13 (s, 2H), 1.34 (s, 6 H); $^{13}C\{^1H\}$ NMR (100 MHz, methanol-d_4) δ 167.5, 164.8, 133.7 (2C), 122.2, 118.8 (2C), 82.7, 70.5, 31.0 (2C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{14}NO_2$ 192.1019, found 192.1027.

*4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-iodophenyl Pivalate (**10a**).* Following TP4, 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl pivalate (**6a**, 137.5 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **10a** (158.4 mg, 80%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.4, 2.2 Hz, 1H), 4.15 (s, 2H), 1.40 (s, 6H), 1.28 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.2, 162.1, 152.2, 133.1, 131.4, 131.0, 121.1, 94.2, 79.4, 68.2, 39.1, 28.2 (2C), 27.0 (3C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{21}INO_3$ 402.0561, found 402.0559.

*4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-(phenylselanyl)-phenyl Pivalate (**10b**).* Following TP4, 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl pivalate (**6b**, 137.5 mg, 0.5 mmol) and diphenyl diselenide (2.02 mg, 0.65 mmol) afforded **10b** (146.5 mg, 62%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.6 Hz, 1H), 7.62−7.60 (m, 2H), 7.33−7.31 (m, 3H), 6.78 (dd, J = 8.6, 2.3 Hz, 1H), 6.41 (d, J = 2.3 Hz, 1H), 4.03 (s, 2H), 1.36 (s, 6H), 1.14 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.4, 160.7, 152.9, 139.9, 137.1 (2C), 130.7, 129.9, 129.6 (2C), 128.9, 123.3 121.8, 118.1, 78.7, 68.6, 38.9, 28.6 (2C), 26.9 (3C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{26}NO_3Se$ 432.1072, found 432.1068.

*tert-Butyl (4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-iodophenyl) Carbonate (**10c**).* Following TP4, *tert*-butyl (4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl) carbonate (**6b**, 145.5, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **10c** (138.3 mg, 70%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 2.3 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.22 (dd, J = 8.4, 2.3 Hz, 1H), 4.13 (s, 2H), 1.55 (s, 9H), 1.41 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 152.0, 150.7, 132.8, 131.5, 131.0, 120.7, 94.1, 84.2, 79.4, 68.2, 28.2 (2C), 27.6 (3C); HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{21}INO_4$ 418.0510, found 418.0499.

*tert-Butyl (4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-(phenylthio)phenyl) Carbonate (**10d**).* Following TP4, *tert*-butyl (4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl) carbonate (**6b**, 145.5 mg, 0.5 mmol) and diphenyl disulfide (141 mg, 0.65 mmol) afforded **10d** (135.6 mg, 68%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: mp 85−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.6 Hz, 1H), 7.55−7.53 (m, 2H), 7.42−7.39 (m, 3H), 6.98 (dd, J = 8.6, 2.3 Hz, 1H), 6.59 (d, J = 2.3 Hz, 1H), 4.09 (s, 2H), 1.48 (s, 9H), 1.42 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 152.7, 150.8, 142.5, 135.0 (2C), 132.7, 131.2, 129.7 (2C), 128.9, 123.0, 120.1, 117.4, 83.9, 78.8, 68.5, 28.4 (2C), 27.6 (3C); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{26}NO_4S$ 400.1577, found 400.1577.

*tert-Butyl (4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-(hydroxy-(phenyl)methyl)phenyl) Carbonate (**10e**).* Following TP4, *tert*-butyl (4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl) carbonate (**6b**, 145,5 mg, 0,5 mmol) and benzaldehyde (0.07 mL, 0.65 mmol) afforded **10e** (119.1 mg, 60%) as a white oil after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 1H), 7.32−7.29 (m, 5H), 7.24 (dd, J = 8.6, 2.3 Hz, 1H), 6.95 (d, J = 2.3 Hz, 1H), 5.91 (s, 1H), 4.03 (d, J = 8.1 Hz, 1H), 3.95 (d, J = 8.1 Hz, 1H), 1.53 (s, 9H), 1.34 (s, 3H), 1.02 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.7, 153.0, 150.9, 146.8, 142.7, 131.9, 127.9 (2C), 126.8, 126.6 (2C), 124.0, 123.0, 119.9, 83.9, 78.8, 74.4, 67.9, 28.3 (2C), 27.6 (3C); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{28}NO_5$ 398.1962, found 398.1967.

https://dx.doi.org/10.1021/acs.joc.0c02369
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*4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-iodophenyl Diethylcarbamate (**10f**).* Following TP4, 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl diethylcarbamate (**6c**,145 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **10f** (166.4, 80%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.67 (m, 2H), 7.16 (dd, J = 8.6, 2.3 Hz, 1H), 4.18 (s, 2H), 3.37−3.28 (m, 4H), 1.42 (s, 6H), 1.19−1.12 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.9, 134.6, 133.6, 131.9, 121.4, 94.0, 80.1, 72.0, 67.2, 57.1, 43.3, 41.9, 27.9 (2C), 14.2, 13.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{22}IN_2O_3$ 417.0670, found 417.0666.

*3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-4-iodophenyl Pivalate (**10g**).* Following TP4, 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl pivalate (**6d**, 137.5 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **10g** (138.3 mg, 69%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 1H), 7.35 (d, J = 2.3 Hz, 1H), 6.88 (dd, J = 8.6, 2.3 Hz, 1H), 4.14 (s, 2H), 1.41 (s, 6H), 1.34 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.3, 161.9, 150.9, 141.0, 135.0, 125.0, 124.0, 89.8, 79.5, 68.2, 39.1, 28.2 (2C), 27.0 (3C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{21}INO_3$ 402.0561, found 402.0561.

*tert-Butyl (3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-iodophenyl) Carbonate (**10h**).* Following TP4, *tert*-butyl (3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl) carbonate (**6e**, 148.5, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **10h** (148.0 mg, 71%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 7.6, 1.8 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.22 (dd, J = 7.8, 1.8 Hz, 1H), 4.15 (s, 2H), 1.57 (s, 9H), 1.42 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.2, 151.8, 150.5, 136.3, 129.0, 127.8, 124.1, 92.5, 84.1, 79.3, 68.1, 28.0 (2C), 27.5 (3C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{21}INO_4$ 418.0510, found 418.0509.

*tert-Butyl (3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-(phenylselanyl)phenyl) Carbonate (**10i**).* Following TP4, *tert*-butyl (3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl) carbonate (**6e**, 148.5, 0.5 mmol) and diphenyl diselenide (202 mg, 0.65 mmol) afforded **10i** (176.6, 79%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 7.4, 1.5 Hz, 1H), 7.18−7.11 (m, 3H), 7.03 (dd, J = 7.4, 1.5 Hz, 1H), 6.96−6.93 (m, 3H), 3.87 (s, 2H), 1.41 (s, 9H), 1.23 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.3, 152.3, 151.1, 135.5, 132.1, 131.5 (2C), 129.5, 129.0 (2C), 128.0, 126.8, 124.8, 124.5, 83.7, 79.5, 67.9, 28.1 (2C), 27.6 (3C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{26}NO_4Se$ 448.1022, found 448.1021.

*3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-iodophenyl Diethylcarbamate (**10j**).* Following TP4, 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl diethylcarbamate (**6f**, 145 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **10j** (112.3 mg, 54%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.28 (m, 2H), 7.16 (dd, J = 7.6, 2.0 Hz, 1H), 4.07 (s, 2H), 3.47 (q, J = 7.1 Hz, 2H), 3.32 (q, J = 7.1 Hz, 2H), 1.34 (s, 6H), 1.24 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.6, 152.6, 152.2, 136.0, 128.7, 127.1, 124.7, 92.6, 79.3, 68.0, 42.2, 41.9, 28.0 (2C), 14.3, 13.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{22}IN_2O_3$ 417.0670, found 417.0677.

*3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-4-iodophenyl Diethylcarbamate (**10k**).* Following TP4, 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl diethylcarbamate (**6f**, 145 mg, 0.5 mmol) and iodine (165 mg, 0.65 mmol) afforded **10k** (52 mg, 25%) as a yellow oil after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 2.8 Hz, 1H), 6.89 (dd, J = 8.6, 2.8 Hz, 1H), 4.08 (s, 2H), 3.34−3.28 (m, 4H), 1.35 (s, 6H), 1.18−1.11 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.2, 153.2, 151.3, 140.8, 134.5, 125.3, 124.3, 89.0, 79.5, 68.0, 42.3, 41.9, 28.1 (2C), 14.1, 13.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{22}IN_2O_3$ 417.0670, found 417.0670.

*Methyl 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-(phenylselanyl)benzoate (**11**).* Following TP4, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (**1a**, 233 mg, 1.0 mmol) and diphenyl diselenide (404 mg, 1.3 mmol) afforded **11** (311.2 mg, 80%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (9:1) as an eluent: mp 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.1 Hz, 1H), 7.77 (dd, J = 8.1, 1.5 Hz, 1H), 7.71−7.68 (m, 2H), 7.58 (d, J = 1.5 Hz, 1H), 7.46−7.40 (m, 3H), 4.13 (s, 2H), 3.77 (s, 3H), 1.47 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.2, 160.7, 138.7, 137.0 (2C), 131.7, 130.2, 129.8, 129.8 (2C), 129.7, 129.6, 129.1, 125.5, 78.9, 68.9, 52.2, 28.6 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{20}NO_3Se$ 390.0603, found 390.0602.

*Methyl 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2,5-bis-(phenylselanyl)benzoate (**12**).* Following TP6, methyl 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-3-(phenylselanyl)benzoate (**11**) (194.5, 0.5 mmol) and diphenyl diselenide (2.02 mg, 0.65 mmol) afforded **12** (130.8 mg, 48%) as a yellow solid after chromatographic purification with hexanes/ethyl acetate (8:2) as an eluent: mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.65 (m, 4H), 7.55 (s, 1H), 7.45−7.39 (m, 6H), 7.35 (s, 1H), 3.92 (s, 2H), 3.75 (s, 3H), 1.36 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5, 160.3, 137.0 (2C), 136.7 (2C), 135.6, 134.4, 131.9, 130.4, 130.1, 129.9, 129.7 (2C), 129.7 (2C), 129.2, 129.1, 128.8, 128.7, 78.8, 68.8, 52.3, 28.5 (2C); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{25}H_{23}NNaO_3Se_2$ 567.9901, found 567.9906

*Synthesis of 4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-(phenylselanyl)-N-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)benzamide (**14**).* In a dry flask under a nitrogen atmosphere and equipped with magnetic stirring, lithium amide **13** was prepared from amine (67.0 mg, 0.33 mmol) in THF (2 mL). The solution was cooled to −78 °C, and *n*-BuLi (2.35 mol/L, 0.14 mL, 0.33 mmol) was added dropwise. After that, the reaction mixture was warmed to 0 °C and left at this temperature for 30 min. 2-Oxazoline **11** (116.4 mg, 0.3 mmol) was then added in THF (2 mL). The solution was stirred at 0 °C for 4 h. Finally, NH_4Cl solution (10 mL) was added. The solution was extracted with dichloromethane (3 × 20 mL). The resulting organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by flash column chromatography with a hexanes/ethyl acetate mixture as an eluent (9:1) to give **14** as a yellow oil (109.0 mg, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.8 Hz, 1H), 7.74−7.72 (m, 1H), 7.64 (dd, J = 8.1, 1.8 Hz, 1H), 7.47−7.42 (m, 2H), 7.29−7.23 (m, 3H), 7.10 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 6.51 (dd, J = 8.3, 2.5 Hz, 1H), 4.14 (s, 2H), 1.64 (s, 4H), 1.48 (s, 6H). 1.24 (s, 6H), 1.23 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.3, 160.6, 145.8, 143.6, 141.5, 139.3, 137.3 (2C), 136.6, 135.3, 135.0, 130.0 (2C), 129.3, 127.3, 126.9, 123.6, 117.8, 113.6, 112.8, 78.9, 68.9, 35.0 (2C), 32.0 (2C), 31.8 (4C), 28.7 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{32}H_{37}N_2O_2Se$ 561.2015, found 561.2016.

*Synthesis of Tamibarotene Derivative (**15**).* In a flask equipped with a magnetic stirring bar, compound **14** (109.0 mg, 0.2 mmol) was dissolved in THF (2.5 mL), and oxalic acid (54.0 mg, 0.6 mmol) was added. The solution was stirred at room temperature for 24 h and then concentrated. The crude product was redissolved in CH_2Cl_2, and the resulting solid was filtered, giving **15** as a yellow oil (93.6 mg, 81%) after chromatographic purification with hexanes/ethyl acetate as an eluent (1:1 to 100% ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.8 Hz, 1H), 7.74−7.63 (m, 4H), 7.42−7.34 (m, 6H), 4.28 (s, 2H), 1.66 (s, 4H), 1.51 (s, 6H), 1.26 (s, 6H), 1.25 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.3, 162.1, 145.7, 141.5, 139.1, 137.7, 136.8 (2C), 135.1, 130.7, 130.0 (2C), 129.4, 128.1, 127.4, 127.1, 124.3, 123.9, 118.0, 117.9, 80.0, 67.8, 35.0 (2C), 31.8 (4C), 29.7 (2C), 28.1 (2C); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{32}H_{39}N_2O_3Se$ 579.2120, found 579.2123.

Computational Studies. We computed the pK_a (Figures 1 and 2) by employing hypothetical reactions between the heterocycle and pyridine (reference) in THF, as described in the literature.[27] We obtained the minima at the potential energy surface by calculating the harmonic frequencies with the B3LYP/6-31+G(d) and B3LYP/6-

https://dx.doi.org/10.1021/acs.joc.0c02369
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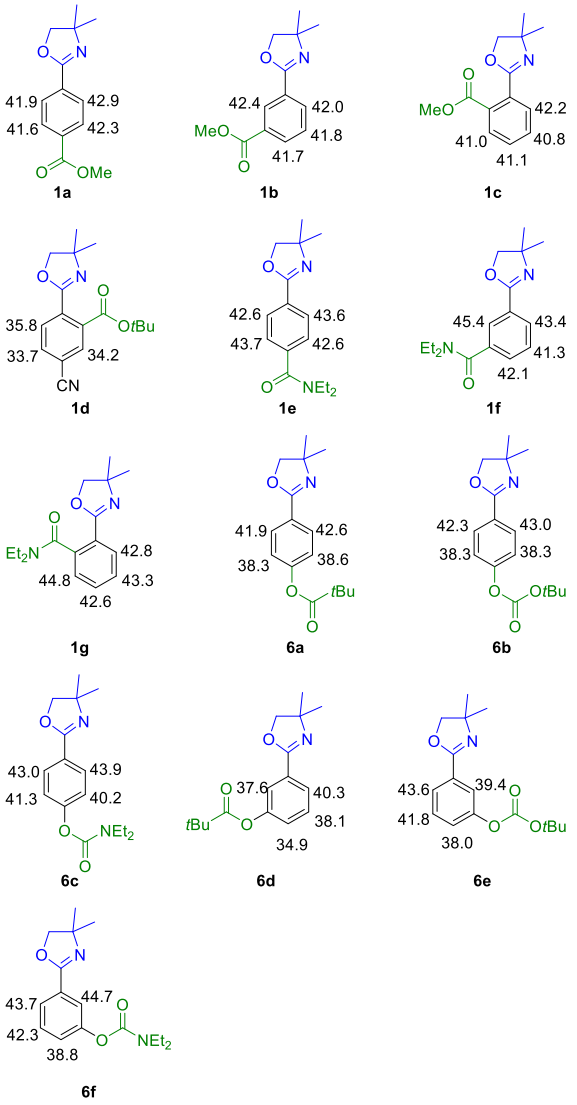

Figure 1. pK_a values calculated for compounds **1a−g** and **6a−f** by using PCM/B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d).

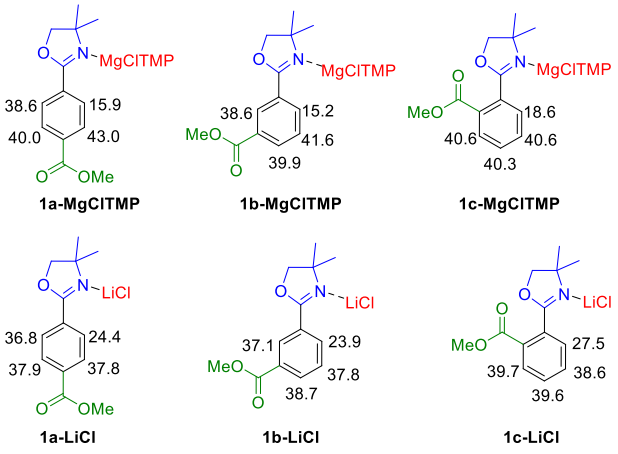

Figure 2. pK_a (THF) values calculated for **1a−c** complexes with TMPMgCl and LiCl complexes with TMPMgCl and LiCl calculated at the B3LYP/6-311++G(d, p)//B3LYP/6-31+G(d,p) level.

31+G(d,p) models.[28] We considered the solvent system by using PCM[29] by single-point calculations on the B3LYP/6-311++G(d,p) model for all molecules. All calculations were performed with the program Gaussian 03.[30] All the outputs were visualized in the software Jmol.[31] Supporting Information contains details of the computational calculations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02369.

^{1}H and ^{13}C NMR spectra and additional data of the computational study are made available (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support for this work by the Brazilian foundations Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Grants 2018/14150-8, 2015/21364-6, and 2014/23604-1), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Conselho Nacional de Desenvolvimento e Tecnológico (CNPq, Grants 140137/2018-1 and 442384/2014-9). Additionally, the authors acknowledge the assistance with HRMS analyses from Dr. Rodrigo Moreira da Silva and Mr. José Carlos Tomaz.

https://dx.doi.org/10.1021/acs.joc.0c02369
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