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Directed Functionalization of Halophenyl-2-oxazolines with TMPMgCl·LiCl

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A variety of difunctionalized aryl-2-oxazolines were prepared from the reaction of halophenyl-2-oxazolines and TMPMgCl·LiCl to give an organomagnesium reagent, which was then treated with various electrophiles. The metalation step takes place under mild conditions, and this process allows for the isolation of the desired products in good yields. No isomeric or other benzyne-derived products were detected. The influence of the halogen substituents on the acidity of the aromatic hydrogen atoms was evaluated by using density functional theory (DFT) calculations.

Introduction

One of the most widespread uses of 2-oxazolines is as a protecting group for carboxylic acids.[1] In addition, 2-oxazoline derivatives have been used in smart polymer engineering[2,3] and in the formation of micelles.[4] The chiral derivatives are widely used as chiral auxiliaries[5] and ligands for asymmetric catalysis, with several applications in organic synthesis.[6] Moreover, the search for new methods to obtain these compounds has gained interest after bioactive molecules that contain a 2-oxazoline unit were found in the marine organisms known as sea squirts (the Ascidiacea class, the Tunicata subphylum).[7] Several oxazoline-containing pattelamides and lissoclinamides were isolated from one of these organisms, *Lissoclinum patella*. Today, more than 100 cyanobactins are known, some of which with remarkable antiviral or cytotoxic activity.[8]

The directed metalation of aromatic and heteroaromatic rings is a powerful method for the preparation of polyfunctionalized unsaturated compounds.[9] Indeed, since Meyers's pioneering work, the *ortho*-lithiation strategy has been widely used for the regioselective functionalization of aryloxazolines.[10] Over the last several years, magnesium and zinc ate bases have been developed for the selective metalation of arenes and heteroarenes.[9c,11] In addition, some of them were applied to the directed functionalization of oxazolines. For example, Marsais and co-workers prepared a number of functionalized heteroaryloxazolines through a directed metalation with lithium alkylmagnesate bases followed by treatment with different electrophiles.[12] Moreover, the full metalation of a 4-bromo-substituted aryloxazoline has been successfully accomplished by Morokuma and co-workers by using the ate base $Bu_2Zn(TMP)Li$ (TMP = 2,2,6,6-tetramethylpiperidyl).[13]

Recently, the mixed Li-Mg amides TMPMgCl·LiCl and $TMP_2Mg·2LiCl$ have proved to be highly active and soluble bases, which allow for the smooth metalation of various substrates and demonstrate an excellent functional group compatibility.[14] In accordance with our interest in the functionalization of aromatic and heterocyclic compounds by using organometallic reagents, we herein report the application of the base TMPMgCl·LiCl in the directed functionalization of halophenyl-2-oxazolines. The electronic effects of substituents attached to the phenyl ring of the substrate were evaluated by calculating the pK_a values of their solutions in tetrahydrofuran (THF) using density functional theory (DFT). The method described herein is an interesting alternative for the preparation of functionalized 2-oxazolines, considering their wide applications in biology and technology.

Results and Discussion

We initiated our study by preparing a number of halophenyl-2-oxazolines from the corresponding aldehydes.[15] Thus, the reaction of 2-amino-2-methylpropanol (**2**) with halophenyl aldehyde **1** followed by an oxidation reaction

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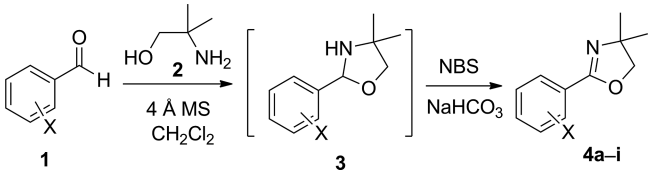
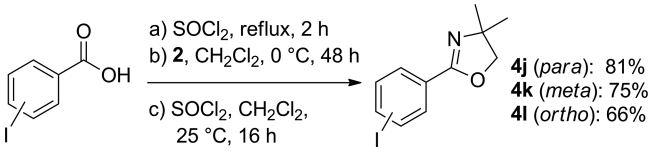
with *N*-bromosuccinimide (NBS) led to the expected oxazoline (i.e., **4a**–**4i**) in moderate to good yield and with high purity (see Scheme 1 and Table 1). In addition, iodo-substituted oxazolines **4j**–**4l** were prepared in 66–81% yield from the corresponding carboxylic acid (see Scheme 2).

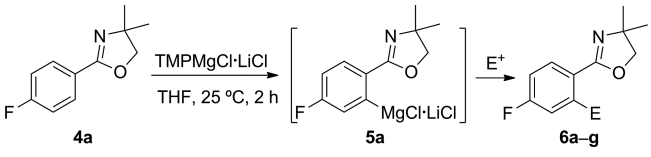


Scheme 1. Preparation of halophenyl-2-oxazolines **4a**–**4i** from aldehydes **1** (MS = molecular sieves).



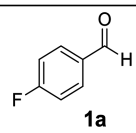
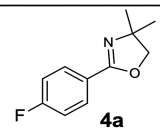
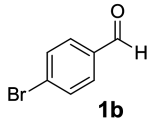
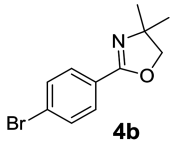
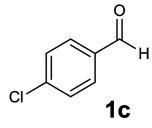
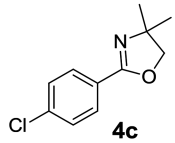
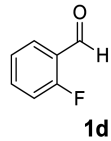
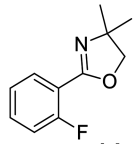
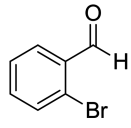
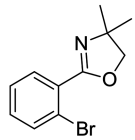
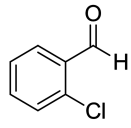
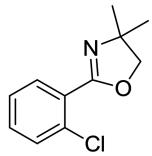
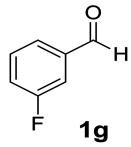
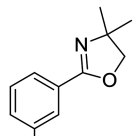
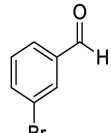
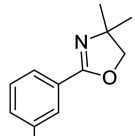
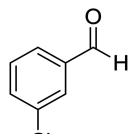
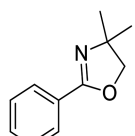
Scheme 2. Preparation of halophenyl-2-oxazolines **4j**–**4l** from carboxylic acid.

To determine the best reaction conditions for the directed magnesiation of the halopheny-2-oxazolines with TMPMgCl·LiCl, we chose 4-fluorophenyl-2-oxazoline **4a**[16] as the model substrate. Thus, after screening for appropriate reaction conditions, the full metalation of **4a** was achieved at 25 °C within 2 h by using 1.8 equiv. of the base. A further reaction of organomagnesium reagent **5a** by treatment with benzaldehyde led to the isolation of alcohol derivative **6a** in 78% yield (see Scheme 3 and Table 2, Entry 1). The reaction of organomagnesium reagent **5a** with iodine and 1,2-dibromotetrachloroethane led to the isolation of the corresponding dihalophenyl-2-oxazolines **6b** and **6c** in 85 and 70% yield, respectively (see Table 2, Entries 2 and 3). The reaction of **5a** with diphenyl diselenide showed the versatility of this system, as it proceeded smoothly to afford phenylselenide derivative **6d** in 90% yield (see Table 2, Entry 4). Palladium-catalyzed coupling reactions are among the most important reactions for the functionalization of aromatic substrates[17] and have already been successfully used for the preparation of 2-oxazoline derivatives. Therefore, we also applied the Negishi cross-coupling reaction for the *ortho*-arylation of 4-fluorophenyl-2-oxazoline (**4a**). After the magnesiation of **4a** by using TMPMgCl·LiCl, organomagnesium reagent **5a** was trans-



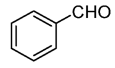
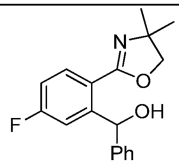
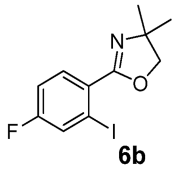
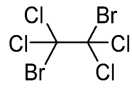
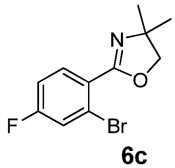
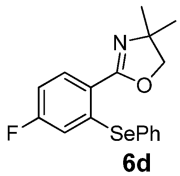
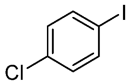
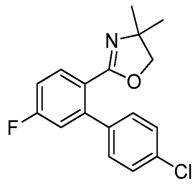
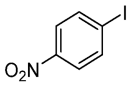
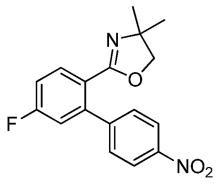
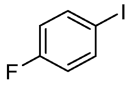
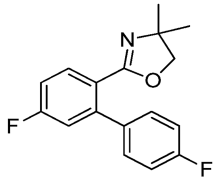
Scheme 3. *ortho*-Metalation of 4-fluorophenyl-2-oxazoline **4a** by using TMPMgCl·LiCl and subsequent reaction with electrophile (E^+).

Table 1. Halophenyl-2-oxazolines **4a**–**4i** obtained from aldehydes **1a**–**1i**.

Entry	Aldehyde	Product	Yield (%) [a]
1	 **1a**	 **4a**	81
2	 **1b**	 **4b**	80
3	 **1c**	 **4c**	79
4	 **1d**	 **4d**	86
5	 **1e**	 **4e**	72
6	 **1f**	 **4f**	82
7	 **1g**	 **4g**	91
8	 **1h**	 **4h**	70
9	 **1i**	 **4i**	90

[a] Isolated yield of analytically pure product.

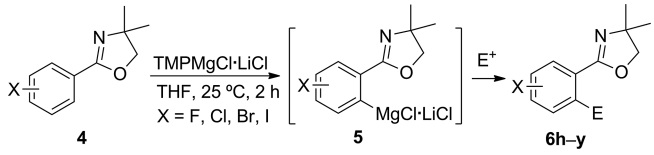
Table 2. Products **6** from directed magnesiation of 4-fluorophenyl-2-oxazoline **4a** with TMPMgCl·LiCl followed by reaction with electrophile.

Entry	E^+	Product	Yield (%)[a]
1		 **6a**	78
2	I_2	 **6b**	85
3		 **6c**	70
4	PhSeSePh	 **6d**	90
5		 **6e**	87[b]
6		 **6f**	85[b]
7		 **6g**	89[b]

[a] Isolated yield of analytically pure product. [b] Obtained by palladium-catalyzed cross-coupling reaction.

metalated with $ZnCl_2$ (1 equiv.) and then treated with 1-chloro-4-iodobenzene in the presence of a mixture of $Pd_2(dba)_3$ (0.8 mol-%, dba = dibenzylideneacetone) and P(*o*-furyl)$_3$ (1.6 mol-%) in THF. After purification, cross-coupling product **6e** was isolated in 87% yield (see Table 2, Entry 5). Similarly, the cross-coupling reactions with 1-iodo-4-nitrobenzene and 1-iodo-4-fluorobenzene led to the *ortho*-arylated derivatives **6f** and **6g** in 85 and 89% yield, respectively (see Table 2, Entries 6 and 7).

The reaction conditions used in Table 2 were then applied to the functionalization of other halophenyl-2-oxazolines. Thus, a number of functionalized 2-oxazolines were prepared in good yields by employing the reaction between the corresponding organomagnesium reagent **5** and different electrophiles (see Scheme 4 and Table 3).

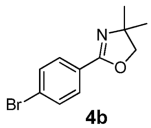
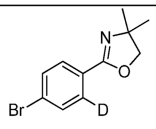
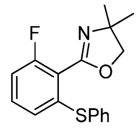
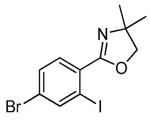
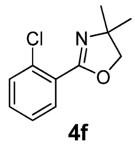
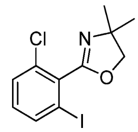
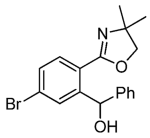
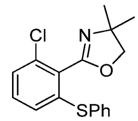
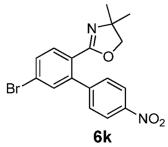
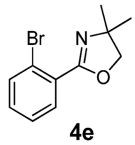
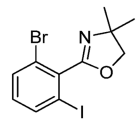
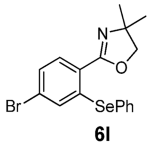
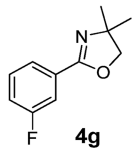
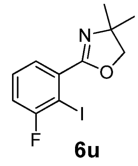
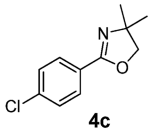
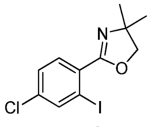
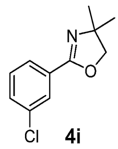
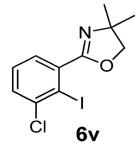
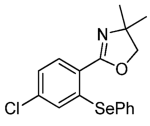
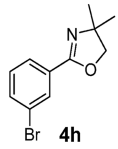
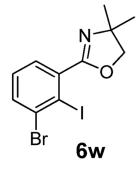
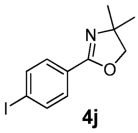
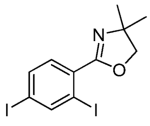
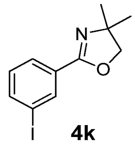
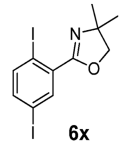
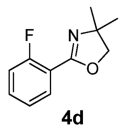
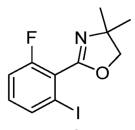
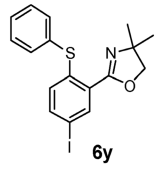


Scheme 4. Synthesis of functionalized 2-oxazolines by using TMPMgCl·LiCl.

The 4-bromo-, 4-chloro- and 4-iodophenyl-2-oxazolines underwent the magnesiation smoothly at room temperature within 2 h. The reaction of the corresponding organomagnesium reagents with different electrophiles led to the desired *ortho*-substituted 4-halophenyl-2-oxazolines **6h**–**6o** in yields that ranged from 60 to 87% (see Table 3, Entries 1–8). Moreover, phenyl-2-oxazolines that contained a fluoro, bromo, or chloro substituent at the *ortho* position were also suitable substrates and afforded 2,6-disubstituted phenyl-2-oxazolines **6p**–**6t** in reasonable to good yields (see Table 3, Entries 9–13). In contrast, attempts to metalate 2-iodophenyl-2-oxazoline **4l** with TMPMgCl·LiCl resulted in low conversion into the expected product.

In the literature, it is well known that the lithiation of aromatic halides may be complicated by the formation of aryne intermediates. Moreover, pioneering studies by Meyers and co-workers have demonstrated that benzyne-oxazolines are easily generated from the corresponding lithiated 3-chlorophenyl-2-oxazolines by warming the reaction mixture from –78 to –15 °C.[18] In contrast, we found that *meta*-fluoro-, *meta*-chloro-, *meta*-bromo- and *meta*-iodophenyl-2-oxazolines were fully metalated at room temperature by using TMPMgCl·LiCl, and no benzyne formation or isomeric products were detected. Upon reaction with the corresponding electrophile, the expected *ortho*-functionalized derivatives were obtained in good yields (see Table 3, Entries 14–18). Interestingly, the metalation of 3-iodophenyl-2-oxazoline **4k** exclusively occurred at the sterically less hindered position, and the reactions with the electrophile yielded 2,5-difunctionalized phenyl-2-oxazolines **6x** and **6y** in 80 and 88% yield, respectively (see Table 3, Entries 17 and 18).

Table 3. Metalation of halophenyl-2-oxazolines with TMPMgCl·LiCl followed by reaction with electrophiles to give **6h**–**6y** .

Entry	Substrate	E^+	Product	Yield (%)[a]	Entry	Substrate	E^+	Product	Yield (%)[a]
1	 **4b**	D_2O	 **6h**	84	10	**4d**	PhSSPh	 **6q**	70
2	**4b**	I_2	 **6i**	71	11	 **4f**	I_2	 **6r**	70
3	**4b**	PhCHO	 **6j**	60	12	**4f**	PhSSPh	 **6s**	68
4	**4b**	p-$IC_6H_4NO_2$	 **6k**	85[b]	13	 **4e**	I_2	 **6t**	55
5	**4b**	PhSeSePh	 **6l**	87	14	 **4g**	I_2	 **6u**	75
6	 **4c**	I_2	 **6m**	60	15	 **4i**	I_2	 **6v**	75
7	**4c**	PhSeSePh	 **6n**	85	16	 **4h**	I_2	 **6w**	70
8	 **4j**	I_2	 **6o**	80	17	 **4k**	I_2	 **6x**	80
9	 **4d**	I_2	 **6p**	80	18	**4k**	PhSSPh	 **6y**	88

[a] Isolated yield of analytically pure product. [b] Obtained by a palladium-catalysed cross-coupling reaction.

The regioselectivity of the metalation of aromatics is governed by a combination of steric and electronic effects. Thus, to rationalize our experimental results, a computational thermochemistry study was performed. The use of computational chemistry to obtain pK_a values is an important tool to guide experimental planning.[19] In addition, this strategy has been used to evaluate the influence of C–H acidity on the regioselectivity of metalations of aromatic and heterocyclic substrates.[20,21] The application of isodesmic reactions diminishes issues that may arise when the pK_a values are directly calculated by deprotonation reactions. As shown in recent studies, the difficulty in obtaining calculated pK_a values close to the experimental values can be overcome by using the appropriate reference compound during the computation.[21] The pK_a values of halophenyl-2-oxazolines **6a**–**6l** in THF were obtained by using the B3LYP method.[22] To evaluate the effect of the halogen substituents, the pK_a values for dehalogenated 2-oxazoline **4m** were also estimated by employing the computational approach (see Figure 1). In the case of the iodophenyl 2-oxazolines, the calculated pK_a values are qualitative and must be used with caution to compare the acidities of the hydrogen atoms that are present in those molecules. Additional details can be found in the Experimental Section and Supporting Information.

As previously reported by Schlosser and co-workers,[20] the presence of halogen substituents has a strong effect on the acidity of the hydrogen atoms that are attached to the aromatic ring. According to our calculations, the most acidic hydrogen atom of halophenyl-2-oxazolines **4** is generally located at the vicinal position to the halogen group (*ortho*-halogen position). This behavior has been observed in most studied compounds and can be attributed to the electron-withdrawing effect of the halogen atom on the aromatic ring. In the case of *meta*-substituted phenyl-2-oxazolines, the hydrogen atom located at the *para* position is slightly more acidic than the one at the *ortho* position. Despite these electronic aspects, the powerful *ortho*-directing effect of the oxazoline group appears to overcome the influence of the halogen substituents and yield highly selective metalations with TMPMgCl·LiCl.

Mulvey and co-workers have investigated the structure of TMPMgCl·LiCl in both the solid state and in solution and have provided insights about the existence of the Lewis acid coordination of the alkali metal with the aromatic substrate in directed *ortho*-metalations.[23] Thus, the observed highly selective metalations of halophenyl-2-oxazolines with TMPMgCl·LiCl may be related to the great ability of the oxazoline group to coordinate to an adjacent lithium atom from the base in solution.

Conclusions

In summary, we have described the directed functionalization of halophenyl-2-oxazolines by using TMPMgCl·LiCl. Metalation takes place under mild conditions to give the corresponding organomagnesium intermediates, which

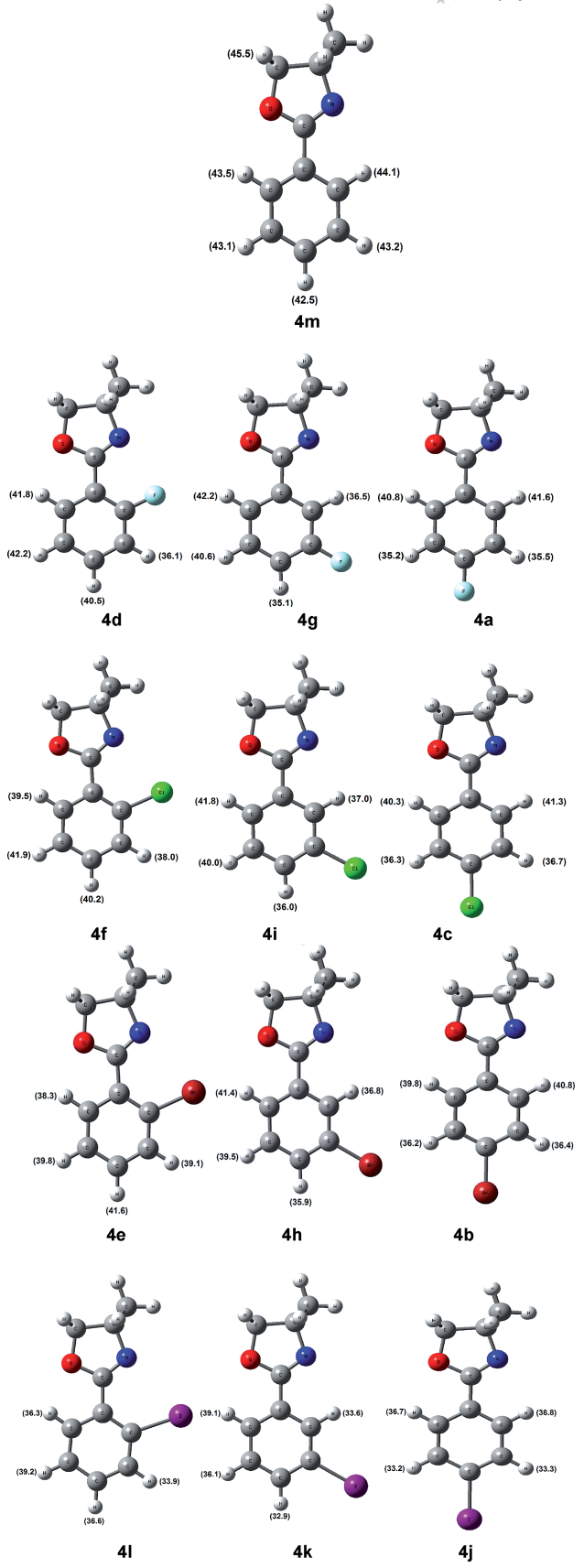


Figure 1. pK_a values for hydrogen atoms calculated using the B3LYP method.

upon treatment with different electrophiles has provided for the synthesis of functionalized 2-oxazolines in good yields without the formation of benzyne or other isomeric structures. As already reported for other haloaromatic compounds, computational calculations show that the halogen substituents of the halophenyl-2-oxazolines have a strong effect on the acidity of their vicinal hydrogen atoms. However, the *ortho*-directing effect of the oxazoline group overcomes this influence from the substituents to allow for highly selective metalation reactions. The scope of this method and its applicability towards the synthesis of biologically active molecules are currently being investigated in our laboratories.

Experimental Section

General Methods: The solvents were purified according to standard procedures.[24] The starting materials were purchased from Sigma Aldrich. All air-sensitive and/or water-sensitive reactions were carried out with dry solvents under anhydrous conditions and under nitrogen. Standard syringe techniques were employed for the transfer of dry solvents and air-sensitive reagents. The reactions were monitored by TLC on Merck silica gel (60 F 254), and the developed plates were visualized by using UV light or 5% vanillin in 10% H_2SO_4 and then heating. Sigma–Aldrich silica gel (particle size 0.040–0.063 nm) was used for flash chromatography. The NMR spectroscopic data were recorded with Bruker DPX 300, 400, and 500 instruments (at 300, 400, and 500 MHz for ^{1}H NMR and at 75, 100, and 125 MHz for ^{13}C NMR), and $CDCl_3$ and [D_6]-DMSO were used as the NMR solvents. The chemical shifts are reported as δ units in parts per million (ppm) relative to the solvent signals as the internal references. Mass spectra (MS) were measured with a Shimadzu GC–MS-QP2010 mass spectrometer. HRMS spectra were measured with a Bruker Daltonics micrOTOF QII/ESI-TOF.

Typical Procedure 1 (TP1). General Procedure for the Preparation of Halophenyl-2-oxazolines 4a–4i: 2-Amino-2-methyl-1-propanol (2.8 mL, 2.6 g, 30.0 mmol) was dissolved in CH_2Cl_2 (180 mL), and the aldehyde (30.0 mmol) was added. The mixture was stirred over MS (4 Å, 15 g) for 14 h. NBS (5.3 g, 30.0 mmol) was then added, and the solution was stirred for an additional 30 min. The mixture was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ (400 mL) and H_2O (100 mL). The organic layer was dried with $MgSO_4$, and the solvent was evaporated. If required, the product was purified by flash column chromatography.

2-(4-Fluorophenyl)-4,4-dimethyl-2-oxazoline (4a): 4-Fluorobenzaldehyde (**1a**, 3.2 mL, 3.7 g, 30.0 mmol) afforded **4a** (4.70 g, 81% yield) as a colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.88 (m, 2 H), 7.00 (m, 2 H), 4.05 (s, 2 H), 1.30 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 164.3 (d, $J_{F,C}$ = 251.8 Hz), 161.1, 130.1 (d, $J_{F,C}$ = 8.9 Hz), 123.5 (d, $J_{F,C}$ = 3.3 Hz), 115.0 (d, $J_{F,C}$ = 22.0 Hz), 79.0, 67.1, 28.0 ppm.

2-(4-Bromophenyl)-4,4-dimethyl-2-oxazoline (4b): 4-Bromobenzaldehyde (**1b**, 5.5 g, 30.0 mmol) afforded **4b** (6.09 g, 80% yield) as a colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.75 (t, J = 2.3 Hz, 1 H), 7.73 (t, J = 1.9 Hz, 1 H), 7.48 (t, J = 2.3 Hz, 1 H), 7.45 (t, J = 1.9 Hz, 1 H), 4.06 (s, 2 H), 1.32 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.1, 131.7, 130.0, 126.7, 126.0, 79.4, 67.7, 28.4 ppm.

2-(4-Chlorophenyl)-4,4-dimethyl-2-oxazoline (4c): 4-Chlorobenzaldehyde (**1c**, 4.2 g, 30.0 mmol) afforded **4c** (4.96 g, 79% yield) as a colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.81 (d, J = 8.54 Hz, 2 H), 7.30 (d, J = 8.54 Hz, 2 H), 4.04 (s, 2 H), 1.31 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.4, 137.5, 129.6, 128.6, 126.4, 79.3, 67.6, 28.4 ppm.

2-(2-Fluorophenyl)-4,4-dimethyl-2-oxazoline (4d): 2-Fluorobenzaldehyde (**1d**, 3.1 mL, 3.7 g, 30.0 mmol) afforded **4d** (4.98 g, 86% yield) as a colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.80 (td, J = 7.59, 1.72 Hz, 1 H), 7.35 (m, 1 H), 7.07 (m, 2 H), 4.03 (s, 2 H), 1.32 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.0 (d, $J_{F,C}$ = 257.8 Hz), 159.0 (d, $J_{F,C}$ = 5.07 Hz), 132.8, 131.2, 123.9 (d, $J_{F,C}$ = 3.58 Hz), 116.5 (d, $J_{F,C}$ = 22.0 Hz), 116.3 (d, $J_{F,C}$ = 11.0 Hz), 78.8, 67.7, 28.3 ppm.

2-(2-Bromophenyl)-4,4-dimethyl-2-oxazoline (4e): 2-Bromobenzaldehyde (**1e**, 3.5 mL, 3.5 g, 30.0 mmol) afforded **4e** (5.48 g, 72% yield) as a colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.60 (dd, J = 7.6, 1.5 Hz, 1 H), 7.55 (dd, J = 7.8, 0.7 Hz, 1 H), 7.27 (dt, J = 14.2, 7.5, 0.7 Hz, 1 H), 7.20 (dt, J = 13.7, 7.8, 1.6 Hz, 1 H), 4.09 (s, 2 H), 1.35 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 162.0, 133.5, 131.6, 131.2, 130.0, 127.0, 121.7, 79.5, 67.8, 28.1 ppm.

2-(2-Chlorophenyl)-4,4-dimethyl-2-oxazoline (4f): 2-Chlorobenzaldehyde (**1f**, 3.4 mL, 4.2 g, 30.0 mmol) afforded **4f** (5.14 g, 82% yield) as a colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.70 (dd, J = 1.7, 7.6 Hz, 1 H), 7.41 (dd, J = 1.0, 8.0 Hz, 1 H), 7.33 (td, J = 1.6, 7.7, 13.6 Hz, 1 H), 7.26 (td, J = 1.6, 7.6, 13.6 Hz, 1 H), 4.13 (s, 2 H), 1.40 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 160.8, 133.1, 131.3, 131.1, 130.3, 127.9, 126.3, 79.1, 67.9, 28.1 ppm.

2-(3-Fluorophenyl)-4,4-dimethyl-2-oxazoline (4g): 2-Fluorobenzaldehyde (**1g**, 3.2 mL, 3.7 g, 30.0 mmol) afforded **4g** (5.26 g, 91% yield) as a colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.71 (dd, J = 1.0, 7.7 Hz, 1 H), 7.62 (dt, J = 1.0, 9.6 Hz, 1 H), 7.35 (m, 1 H), 7.14 (tt, J = 1.5, 8.4, 14.1 Hz, 1 H), 4.10 (s, 2 H), 1.37 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 162.4 (d, $J_{F,C}$ = 246.1 Hz), 130.2 (d, $J_{F,C}$ = 8.33 Hz), 129.9 (d, $J_{F,C}$ = 8.01 Hz), 123.9 (d, $J_{F,C}$ = 3.01 Hz), 118.12 (d, $J_{F,C}$ = 21.40 Hz), 115.2 (d, $J_{F,C}$ = 23.49 Hz), 79.2, 67.7, 28.3 ppm.

2-(3-Bromophenyl)-4,4-dimethyl-2-oxazoline (4h): 3-Bromobenzaldehyde (**1h**, 3.5 mL, 5.5 g, 30.0 mmol) afforded **4h** (5.33 g, 70% yield). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.03 (t, J = 1.5 Hz, 1 H), 7.80 (dt, J = 7.9, 1.2 Hz, 1 H), 7.51 (m, 1 H), 7.20 (t, J = 8.0 Hz, 1 H), 4.05 (s, 2 H), 1.31 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.0, 134.2, 131.2, 130.0, 126.7, 122.3, 79.3, 67.6, 28.3 ppm.

2-(3-Chlorophenyl)-4,4-dimethyl-2-oxazoline (4i): 3-Chlorobenzaldehyde (**1i**, 3.4 mL, 4.2 g, 30.0 mmol) afforded **4i** (5.65 g, 90% yield) as a colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.86 (t, J = 1.51 Hz, 1 H), 7.72 (dt, J = 7.80, 1.15 Hz, 1 H), 7.34 (m, 1 H), 7.23 (t, J = 7.90 Hz, 1 H), 4.02 (s, 2 H), 1.30 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 160.9, 134.4, 131.2, 129.6, 128.3, 126.3, 79.3, 67.7, 28.4 ppm.

Typical Procedure 2 (TP2). General Procedure for the Preparation of Iodophenyl-2-oxazolines (4j–4l): A mixture of iodobenzoic acid (7.44 g, 30.0 mmol) and thionyl chloride (4.37 mL, 7.13 g, 60.0 mmol) was stirred at 25 °C for 24 h. The excess amount of thionyl chloride was removed by distillation, and the remaining dark oil was dissolved in dichloromethane (40 mL). The resulting solution was then added dropwise to a magnetically stirred solution of 2-amino-2-methyl-1-propanol (**2**, 4.5 mL, 4.2 g, 47.8 mmol) in dichloromethane (40 mL) at 0 °C. The mixture was stirred at 25 °C for 2 h. The resulting white precipitate was collected by filtration

and washed with water. The dichloromethane layer of the filtrate was concentrated and cooled, and the resulting precipitate was collected by filtration. To the obtained *N*-(2,2-dimethyl-3-hydroxypropyl)iodobenzamide was added thionyl chloride (5.34 g, 45 mmol) dropwise as the mixture was stirred. The excess amount of thionyl chloride was removed by distillation, and dry ether (100 mL) was added. The solution was washed with 20% sodium hydroxide (2× 30 mL). The organic phase was dried with K_2CO_3, filtered, and concentrated under vacuum to give the corresponding iodo-2-oxazoline.

2-(4-Iodophenyl)-4,4-dimethyl-2-oxazoline (4j): Pale yellow oil (5.61 g, 81% yield). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.75 (d, J = 8.6 Hz, 2 H), 7.65 (d, J = 8.6 Hz, 2 H), 4.10 (s, 2 H), 1.37 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.5, 137.5, 129.8, 127.5, 98.1, 79.2, 67.7, 28.3 ppm.

2-(3-Iodophenyl)-4,4-dimethyl-2-oxazoline (4k): Pale yellow oil (5.20 g, 75% yield). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.31 (s, 1 H), 7.88 (d, J = 7.8 Hz, 1 H), 7.79 (d, J = 7.8 Hz, 1 H), 7.13 (t, J = 7.8 Hz, 1 H), 4.10 (s, 2 H), 1.38 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 160.6, 140.0, 136.9, 129.9, 129.8, 127.3, 93.8, 79.2, 67.7, 28.3 ppm.

2-(2-Iodophenyl)-4,4-dimethyl-2-oxazoline (4l): Yellow oil (5.65 g, 66% yield). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.90 (d, J = 8.0 Hz, 1 H), 7.57 (d, J = 7.5 Hz, 1 H), 7.37 (t, J = 7.5 Hz, 1 H), 7.10 (m, 1 H), 4.15 (s, 2 H), 1.42 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 162.8, 140.1, 134.2, 131.4, 130.5, 127.7, 94.7, 79.4, 68.2, 28.2 ppm.

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 (1.12 M in THF, 44.64 mL, 50.0 mmol), and then 2,2,6,6-tetramethylpiperidine (9.2 mL, 55.0 mmol) was added dropwise through a syringe within 5 min. The mixture was stirred until the gas evolution ceased (24–48 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 0.9 to 1.1 M.

Typical Procedure 4 (TP4). Metalation of Halophenyl-2-oxazolines: A flame-dried and argon-flushed Schlenk tube equipped with a rubber septum and a magnetic stirring bar was charged with a solution of the halophenyl-2-oxazoline (0.5 mmol) in dry THF (1 mL). The mixture was warmed to 25 °C, and then TMPMgCl·LiCl (0.98 M in THF, 1.02 mL, 1.0 mmol) was added dropwise through a syringe. The mixture was stirred at the given temperature for the indicated time. The completion of the metalation was monitored by GC analysis of reaction aliquots that were quenched with I_2 in dry THF. Thus, a solution of the indicated electrophile in THF (1.0 mL) was added dropwise and the reaction mixture stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), the products were extracted with ethyl acetate (3× 10 mL), the extracts washed with brine, dried with $MgSO_4$, and concentrated.

[2-(4,4-Dimethyl-2-oxazoline)-5-fluorophenyl](phenyl)-methanol (6a): 2-(4-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4a**, 96.6 mg, 0.5 mmol) and benzaldehyde (0.10 mL, 106 mg, 1.0 mmol) afforded **6a** (115.4 mg, 78% yield) as a light yellow solid; m.p. 70–72 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.80 (dd, J = 8.7, 5.8 Hz, 1 H), 7.21 (m, 5 H), 6.96 (dq, J = 13.7, 7.9, 2.7, 0.7 Hz, 1 H), 6.74 (d, J = 9.8, 2.7 Hz, 1 H), 5.86 (s, 1 H), 3.98 (d, J = 8.1 Hz, 1 H), 3.90 (d, J = 8.1 Hz, 1 H), 1.28 (s, 3 H), 1.00 (s, 3 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 164.1 (d, $J_{F,C}$ = 253.4 Hz), 161.5, 148.1 (d, $J_{F,C}$ = 6.9 Hz), 142.2, 132.78 (d, $J_{F,C}$ = 8.7 Hz), 128.0, 127.0, 126.6, 122.8, 117.5 (d, $J_{F,C}$ = 22.8 Hz), 114.2 (d, $J_{F,C}$ = 20.6 Hz), 78.7, 73.9, 67.9, 28.3, 27.7 ppm. IR (KBr): $\tilde{\nu}$ = 3214, 2975, 1671, 1321, 1040, 704 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{19}FNO_2$ [M + H]$^+$ 300.1400; found 300.1394.

2-(4-Fluoro-2-iodophenyl)-4,4-dimethyl-2-oxazoline (6b): 2-(4-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4a**, 96.6 mg, 0.5 mmol) and iodine (254 mg, 1.0 mmol) afforded **6b** (134.3 mg, 85% yield) as a dark yellow solid; m.p. 65–67 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.54 (m, 2 H), 7.02 (td, J = 13.9, 8.2, 2.6 Hz, 1 H), 4.08 (s, 2 H), 1.35 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 163.1 (d, $J_{F,C}$ = 184.5 Hz), 161.5, 132.0 (d, $J_{F,C}$ = 8.5 Hz), 130.2 (d, $J_{F,C}$ = 3.8 Hz), 127.4 (d, $J_{F,C}$ = 23.8 Hz), 115.1 (d, $J_{F,C}$ = 21.6 Hz), 94.6 (d, $J_{F,C}$ = 8.6 Hz), 79.5, 68.2, 28.2 ppm.

2-(2-Bromo-4-fluorophenyl)-4,4-dimethyl-2-oxazoline (6c): 2-(4-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4a**, 96.6 mg, 0.5 mol) and 1,2-dibromoethane (0.086 mL, 187.0 mg, 1.0 mmol) afforded **6c** (94.5 mg, 70% yield) as a dark yellow solid; m.p. 68–70 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.61 (dd, J = 6.0, 2.70 Hz, 1 H), 7.30 (dd, J = 8.30, 2.50 Hz, 1 H), 7.00 (dq, J = 14.0, 5.30, 2.60, 0.80 Hz, 1 H), 4.07 (s, 2 H), 1.34 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 163.1 (d, $J_{F,C}$ = 255.2 Hz), 161.0, 132.8 (d, $J_{F,C}$ = 9.0 Hz), 126.4 (d, $J_{F,C}$ = 3.6 Hz), 122.5 (d, $J_{F,C}$ = 10.0 Hz), 121.2 (d, $J_{F,C}$ = 24.5 Hz), 114.4 (d, $J_{F,C}$ = 21.5 Hz), 79.5, 68.1, 28.2 ppm.

2-[4-Fluoro-2-(phenylselenyl)phenyl]-4,4-dimethyl-2-oxazoline (6d): 2-(4-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4a**, 96.6 mg, 0.5 mmol) and diphenyl diselenide (312.1 mg, 1.0 mmol) afforded **6d** (155.5 mg, 90% yield) as a dark yellow solid; m.p. 70–72 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.75 (t, J = 6.7 Hz, 1 H), 7.61 (dt, J = 6.30, 1.40 Hz, 2 H), 7.36 (m, 3 H), 6.75 (dq, J = 14.0, 6.0, 2.60, 0.60 Hz, 1 H), 6.47 (dd, J = 10.1, 2.6 Hz, 1 H), 4.05 (s, 2 H), 1.39 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 164.0 (d, $J_{F,C}$ = 252.6 Hz), 160.8, 141.6 (d, $J_{F,C}$ = 7.8 Hz), 137.3, 136.3, 131.6 (d, $J_{F,C}$ = 10.0 Hz), 129.9, 129.4, 121.8, 116.0 (d, $J_{F,C}$ = 25.1 Hz), 112.1 (d, $J_{F,C}$ = 22.3 Hz), 78.9, 79.5, 68.6, 28.6 ppm. IR (KBr): $\tilde{\nu}$ = 2961, 1644, 1559, 1489, 1027, 746 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{17}FNOSe$ [M + H]$^+$ 350.0459; found 350.0459.

2-(4-Bromo-2-deuterophenyl)-4,4-dimethyl-2-oxazoline (6h): 2-(4-Bromophenyl)-4,4-dimethyl-2-oxazoline (**4b**, 127.0 mg, 0.5 mmol) and D_2O (0.018 mL, 20.0 mg, 1.0 mmol) afforded **6h** (107.1 mg, 84% yield) as a yellow solid; m.p. 186–187 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.74 (d, J = 8.7 Hz, 1 H), 7.47 (m, 2 H), 4.05 (s, 2 H),1.32 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.5, 131.5, 129.8, 126.2, 79.3, 67.6, 59.9, 28.3 ppm. IR (KBr): $\tilde{\nu}$ = 3395, 2933, 1629, 1391, 1013, 760 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{21}DBrNO$ [M + H]$^+$ 255.0243; found 255.0238.

2-(4-Bromo-2-iodophenyl)-4,4-dimethyl-2-oxazoline (6i): 2-(4-Bromophenyl)-4,4-dimethyl-2-oxazoline (**4b**, 127.0 mg, 0.5 mmol) and iodine (254 mg, 1.0 mmol) afforded **6i** (134.1 mg, 71% yield) as a light brown solid; m.p. 67–69 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.01 (d, J = 1.8 Hz, 1 H), 7.44 (dd, J = 8.2, 1.8 Hz, 1 H), 7.38 (d, J = 8.2 Hz, 1 H), 4.06 (s, 2 H), 1.34 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.9, 142.3, 133.0, 131.4, 131.0, 124.8, 95.2, 79.4, 68.3, 28.2 ppm.

[5-Bromo-2-(4,4-dimethyl-2-oxazoline)phenyl](phenyl)methanol (6j): 2-(4-Bromophenyl)-4,4-dimethyl-2-oxazoline (**4b**, 127.0 mg, 0.5 mmol) and benzaldehyde (0.10 mL, 106 mg, 1.0 mmol) afforded **6j** (108.0 mg, 60% yield) as a white oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.66 (d, J = 8.3 Hz, 1 H), 7.43 (d, J = 8.3, 2.0 Hz, 1 H), 7.25 (d, J = 2.0 Hz, 1 H), 7.23 (m, 3 H), 7.19 (m, 1 H), 5.81 (s, 1 H), 3.96 (d, J = 8.2 Hz, 1 H), 3.87 (d, J = 8.2 Hz, 1 H), 1.26 (s, 3 H), 0.94 (s, 3 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.7, 146.7, 142.5, 133.3, 132.0, 130.6, 127.9, 126.5, 126.1, 125.6, 78.8, 74.3,

68.0, 28.3, 27.7 ppm. IR (KBr): ṽ = 3199, 2961, 1644, 1307, 1027, 732 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{19}BrNO_2$ [M + H]$^+$ 360.0599; found 359.0593.

2-[4-Bromo-2-(phenylselenyl)phenyl]-4,4-dimethyl-2-oxazoline (6l): 2-(4-Bromophenyl)-4,4-dimethyl-2-oxazoline (**4b**, 127.0 mg, 0.5 mmol) and diphenyl diselenide (312.1 mg, 1.0 mmol) afforded **6l** (178.0 mg, 87% yield) as a green solid; m.p. 98–100 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.61 (m, 3 H), 7.36 (m, 3 H), 7.20 (dd, J = 8.4, 2.0 Hz, 1 H), 6.89 (d, J = 1.9 Hz, 1 H), 4.05 (s, 2 H), 1.39 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 160.9, 140.6, 137.0, 135.1, 131.3, 129.9, 129.3, 127.9, 127.7, 124.4, 78.9, 68.6, 28.5, 27.7 ppm. IR (KBr): ṽ = 2962, 1636, 1466, 1041, 737 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{17}BrNOSe$ [M + H]$^+$ 409.9659; found 409.9653.

2-(4-Chloro-2-iodophenyl)-4,4-dimethyl-2-oxazoline (6m): 2-(4-Chlorophenyl)-4,4-dimethyl-2-oxazoline (**4c**, 105.0 mg, 0.5 mmol) and iodine (254 mg, 1.0 mmol) afforded **6m** (100.0 mg, 60% yield) as a yellow solid; m.p. 65–67 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.92 (d, J = 2.0 Hz, 1 H), 7.52 (d, J = 8.3 Hz, 1 H), 7.35 (dd, J = 2.0, 8.3 Hz, 1 H), 4.14 (s, 2 H), 1.41 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.8, 139.7, 136.6, 132.5, 131.2, 128.1, 94.8, 79.4, 68.3, 28.2 ppm.

2-[4-Chloro-2-(phenylselenyl)phenyl]-4,4-dimethyl-2-oxazoline (6n): 2-(4-Chlorophenyl)-4,4-dimethyl-2-oxazoline (**4c**, 105.0 mg, 0.5 mmol) and diphenyl diselenide (312.1 mg, 1.0 mmol) afforded **6n** (155.0 mg, 85% yield) as a yellow oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.70 (m, 3 H), 7.43 (m, 3 H), 7.09 (dd, J = 2.0, 8.3 Hz, 1 H), 6.82 (d, J = 2.0 Hz, 1 H), 4.09 (s, 2 H), 1.44 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 160.4, 140.3, 137.0, 130.6, 129.8, 129.2, 128.4, 124.8, 124.2, 78.7, 68.7, 28.6 ppm. IR (KBr): ṽ = 2961, 1629, 1461, 1321, 1027, 732 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{17}ClNOSe$ [M + H]$^+$ 366.0164; found 366.0160.

2-(2,4-Diiodophenyl)-4,4-dimethyl-2-oxazoline (6o): 2-(4-Iodophenyl)-4,4-dimethyl-2-oxazoline (**4j**, 105.0 mg, 0.5 mmol) and iodine (254.0 mg, 1.0 mmol) afforded **6o** (169.0 mg, 80% yield) as a dark yellow solid; m.p. 73–75 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.28 (d, J = 1.7 Hz, 1 H), 7.70 (dd, J = 8.0, 1.7 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 4.13 (s, 2 H), 1.41 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 162.1, 147.8, 136.9, 133.5, 131.6, 97.0, 95.5, 79.4, 68.3, 28.2 ppm. IR (KBr): ṽ = 3437, 2961, 1658, 1083, 1013, 802 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}I_2NO$ [M + H]$^+$ 427.9008; found 427.9007.

2-(2-Fluoro-6-iodophenyl)-4,4-dimethyl-2-oxazoline (6p): 2-(2-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4d**, 96.6 mg, 0.5 mmol) and iodine (254 mg, 1.0 mmol) afforded **6p** (126.4 mg, 80% yield) as a yellow solid; m.p. 67–69 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.57 (m, 1 H), 7.20 (s, 1 H), 7.03 (m, 1 H), 4.10 (s, 2 H), 1.38 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.3, 158.8 (d, $J_{F,C}$ = 6.5 Hz), 134.8 (d, $J_{F,C}$ = 3.6 Hz), 132.5 (d, $J_{F,C}$ = 8.7 Hz), 123.8 (d, $J_{F,C}$ = 17.8 Hz), 115.6 (d, $J_{F,C}$ = 21.4 Hz), 96.4, 79.1, 68.5, 28.1 ppm.

2-[2-Fluoro-6-(phenylthio)phenyl]-4,4-dimethyl-2-oxazoline (6q): 2-(2-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4d**, 96.6 mg, 0.5 mmol) and diphenyl disulfide (218 mg, 1.0 mmol) afforded **6q** (104.3 mg, 70% yield) as a white solid; m.p. 70–72 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.39 (m, 2 H), 7.29 (m, 3 H), 7.11 (td, J = 8.1, 5.8 Hz, 1 H), 6.84 (t, J = 8.7 Hz, 1 H), 6.70 (d, J = 8.1 Hz, 1 H), 4.07 (s, 2 H), 1.37 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 162.1, 158.5 (d, $J_{F,C}$ = 223.8 Hz), 140.8 (d, $J_{F,C}$ = 2.3 Hz), 133.6, 133.2, 131.4 (d, $J_{F,C}$ = 9.2 Hz), 129.5, 128.4, 124.9 (d, $J_{F,C}$ = 3.3 Hz), 113.1 (d, $J_{F,C}$ = 21.7 Hz), 79.3, 68.3, 28.2 ppm. IR (KBr): ṽ = 2961, 1658, 1433, 1237, 1054, 746 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{17}FNOS$ [M + H]$^+$ 302.1015; found 302.1020.

2-(2-Chloro-6-iodophenyl)-4,4-dimethyl-2-oxazoline (6r): 2-(2-Chlorophenyl)-4,4-dimethyl-2-oxazoline (**4f**, 104.0 mg, 0.5 mmol) and iodine (254 mg, 1.0 mmol) afforded **6r** (116.2 mg, 70% yield) as a yellow oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.65 (dd, J = 8.0, 1.0 Hz, 1 H), 7.30 (dd, J = 8.0, 1.0 Hz, 1 H), 6.94 (t, J = 8.0 Hz, 1 H), 4.09 (s, 2 H), 1.37 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 160.7, 137.2, 133.4, 131.6, 129.0, 96.5, 79.5, 68.4, 26.9 ppm. IR (KBr): ṽ = 2961, 1671, 1433, 1293, 1111, 1040, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}ClNO$ [M + H]$^+$ 335.9652; found 335.9666.

2-[2-Chloro-6-(phenylthio)phenyl]-4,4-dimethyl-2-oxazoline (6s): 2-(2-Chlorophenyl)-4,4-dimethyl-2-oxazoline (**4f**, 104.0 mg, 0.5 mmol) and diphenyl disulfide (218 mg, 1.0 mmol) afforded **6s** (106.7 mg, (68% yield) as a light yellow solid; m.p. 67–69 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.37 (m, 2 H), 7.26 (m, 2 H), 7.16 (dd, J = 8.0, 1.1 Hz, 1 H), 7.08 (t, J = 8.0 Hz, 1 H), 6.89 (dd, J = 8.0, 1.1 Hz, 1 H), 4.09 (s, 2 H), 1.38 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 159.1, 139.8, 133.6, 133.0, 130.8, 129.4, 128.2, 127.2, 79.5, 68.4, 28.0 ppm. IR (KBr): ṽ = 3073, 2961, 1658, 1433, 1293, 1040, 956, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{17}ClNOS$ [M + H]$^+$ 318.0719; found 318.0714.

2-(2-Bromo-6-iodophenyl)-4,4-dimethyl-2-oxazoline (6t): 2-(2-Bromophenyl)-4,4-dimethyl-2-oxazoline (**4e**, 127.0 mg, 0.5 mmol) and iodine (254 mg, 1.0 mmol) afforded **6t** (104.0 mg, 55% yield) as a yellow solid; m.p. 78–80 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.67 (m, 2 H), 7.16 (dd, J = 8.4, 2.4 Hz, 1 H), 4.08 (s, 2 H), 1.35 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.6, 141.8, 135.7, 134.5, 133.4, 122.1, 92.5, 79.6, 68.3, 28.1 ppm. IR (KBr): ṽ = 2961, 1671, 1293, 1013, 802 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}BrINO$ [M + H]$^+$ 379.9147; found 379.9145.

2-(3-Fluoro-2-iodophenyl)-4,4-dimethyl-2-oxazoline (6u): 2-(3-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4g**, 96.6 mg, 0.5 mmol) and iodine (254 mg, 1.0 mmol) afforded **6u** (118.5 mg, 75% yield) as a dark yellow solid; m.p. 65–67 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.74 (m, 2 H), 7.25 (t, J = 7.6 Hz, 1 H), 4.15 (s, 2 H), 1.32 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.5, 141.5, 135.8, 134.5, 133.4, 122.1, 92.6, 79.6, 68.3, 28.2 ppm. IR (KBr): ṽ = 2919, 1671, 1447, 971, 788 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{11}FINO$ [M + H]$^+$ 319.9948; found 319.9943.

2-(3-Chloro-2-iodophenyl)-4,4-dimethyl-2-oxazoline (6v): 2-(3-Chlorophenyl)-4,4-dimethyl-2-oxazoline (**4i**, 104.0 mg, 0.5 mmol) and iodine (254 mg, 1.0 mmol) afforded **6v** (126.0 mg, 75% yield). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.28 (m, 2 H), 7.06 (dd, J = 7.7, 2.3 Hz, 1 H), 4.10 (s, 2 H), 1.36 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 163.5, 162.1, 160.2, 136.3, 129.8, 126.2, 117.0, 79.5, 68.2, 28.2 ppm. IR (KBr): ṽ = 3241, 2947, 1742, 1644, 1405, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}ClINO$ [M + H]$^+$ 335.9642; found 335.9648.

2-(3-Bromo-2-iodophenyl)-4,4-dimethyl-2-oxazoline (6w): 2-(3-Bromophenyl)-4,4-dimethyl-2-oxazoline (**4h**, 127.0 mg, 0.5 mmol) and iodine (254 mg, 1.0 mmol) afforded **6w** (133.0 mg, 70% yield) as a yellow oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.67 (m, 2 H), 7.16 (dd, J = 8.4, 2.4 Hz, 1 H), 4.07 (s, 2 H), 1.34 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.5, 141.4, 135.7, 134.5, 133.4, 122.1, 92.6, 79.5, 68.3, 28.2 ppm. IR (KBr): ṽ = 2947, 1671, 1307, 1069, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}BrINO$ [M + H]$^+$ 379.9147; found 379.9142.

2-(5-Iodo-3-iodophenyl)-4,4-dimethyl-2-oxazoline (6x): 2-(3-Iodophenyl)-4,4-dimethyl-2-oxazoline (**4k**, 105.0 mg, 0.5 mmol) and iodine (254.0 mg, 1.0 mmol) afforded **6x** (169.0 mg, 80% yield) as

a yellow oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.90 (d, J = 2.1 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 1 H), 7.40 (dd, J = 8.3, 2.1 Hz, 1 H), 4.14 (s, 2 H), 1.41 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 161.3, 141.5, 140.3, 139.1, 135.9, 93.2, 93.0, 79.5, 68.3, 28.1 ppm. IR (KBr): $\tilde{\nu}$ = 2961, 1644, 1293, 998, 802 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}I_2NO$ $[M + H]^+$ 427.9008; found 427.9003.

2-[3-Iodo-2-(phenylthio)phenyl]-4,4-dimethyl-2-oxazoline (6y): 2-(3-Iodophenyl)-4,4-dimethyl-2-oxazoline (**4k**, 105.0 mg, 0.5 mmol) and diphenyl disulfide (312.1 mg, 1.0 mmol) afforded **6y** (178.0 mg, 88% yield) as a yellow solid; m.p. 78–80 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.07 (d, J = 1.5 Hz, 1 H), 7.51 (m, 2 H), 7.45 (dd, J = 8.5, 1.6 Hz, 1 H), 7.39 (m, 3 H), 6.56 (d, J = 8.5 Hz, 1 H), 4.09 (s, 2 H), 1.42 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 166.0, 140.6, 139.3, 138.4, 132.8, 129.7, 129.6, 128.9, 88.6, 78.9, 68.6, 28.4 ppm. IR (KBr): $\tilde{\nu}$ = 2947, 1644, 1349, 1027, 830 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{17}INOS$ $[M + H]^+$ 410.0076; found 410.0074.

Typical Procedure 5 (TP5). Quenching by Negishi Cross-Coupling Reaction: After complete metalation according to TP4, a solution of $ZnCl_2$ in THF was added (1 M in THF, 0.5 mL, 0.5 mmol). After 15 min, a solution of $Pd(PPh_3)_4$ (0.8 mol-%, 4.5 mg) in THF (1 mL) and a solution of corresponding aryl halide RX (1 mmol, 2 equiv.) 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 AcOEt (3× 40 mL). The solvent of the combined organic layers was evaporated under vacuum, and the product was purified by flash column chromatography.

2-(4′-Chloro-5-fluoro-[1,1′-biphenyl]-2-yl)-4,4-dimethyl-2-oxazoline (6e): 2-(4-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4a**, 96.6 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (238.4 mg, 1.0 mmol) afforded **6e** (130.5 mg, 87% yield) as a brown oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.72 (dd, J = 8.6, 5.8 Hz, 1 H), 7.31 (t, J = 2.0 Hz, 1 H), 7.28 (t, J = 2.0 Hz, 1 H), 7.23 (t, J = 2.0 Hz, 1 H), 7.21 (t, J = 2.0 Hz, 1 H), 7.03 (dd, J = 8.3, 2.6 Hz, 1 H), 6.98 (m, 1 H), 3.76 (s, 2 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 164.0 (d, $J_{F,C}$ = 189.0 Hz), 162.4, 143.1 (d, $J_{F,C}$ = 8.6 Hz), 138.4, 134.0, 132.7 (d, $J_{F,C}$ = 8.8 Hz), 129.5, 128.3, 123.5 (d, $J_{F,C}$ = 2.3 Hz), 117.1 (d, $J_{F,C}$ = 22.4 Hz), 114.6 (d, $J_{F,C}$ = 21.4 Hz), 79.7, 67.3, 27.9 ppm. IR (KBr): $\tilde{\nu}$ = 2961, 1658, 1461, 1293, 1181, 1096, 830 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{16}ClFNO$ $[M + H]^+$ 304.0904; found 304.0910.

2-(5-Fluoro-4′-nitro-[1,1′-biphenyl]-2-yl)-4,4-dimethyl-2-oxazoline (6f): 2-(4-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4a**, 96.6 mg, 0.5 mmol) and 1-iodo-4-nitrobenzene (249.0 mg, 1.0 mmol) afforded **6f** (128.2 mg, 85% yield) as a dark brown solid; m.p. 83–85 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.20 (dt, J = 8.8, 2.0 Hz, 2 H), 7.85 (dd, J = 8.6 Hz, 5.6 Hz, 1 H), 7.45 (dt, J = 8.6, 2.0 Hz, 2 H), 7.11 (td, J = 8.2, 2.0 Hz, 1 H), 7.01 (dd, J = 9.0, 2.5 Hz, 1 H), 3.79 (s, 2 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 163.8 (d, $J_{F,C}$ = 254.2 Hz), 149.0 (d, $J_{F,C}$ = 8.7 Hz), 147.3, 146.6, 142.2 (d, $J_{F,C}$ = 8.1 Hz), 133.1 (d, $J_{F,C}$ = 9.0 Hz), 129.2, 123.3, 117.3 (d, $J_{F,C}$ = 22.9 Hz), 115.6 (d, $J_{F,C}$ = 21.2 Hz), 79.8, 67.5, 27.1 ppm. IR (KBr): $\tilde{\nu}$ = 2975, 1602, 1517, 1349, 844 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{16}FN_2O_3$ $[M + H]^+$ 315.1145; found 314.1140.

2-(4′,5-Difluoro-[1,1′-biphenyl]-2-yl)-4,4-dimethyl-2-oxazoline (6g): 2-(4-Fluorophenyl)-4,4-dimethyl-2-oxazoline (**4a**, 96.6 mg, 0.5 mmol) and 4-fluoroiodobenzene (0.11 mL, 222.0 mg, 1.0 mmol) afforded **6g** (127.0 mg, 89% yield) as a dark brown oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.70 (t, J = 5.0 Hz, 1 H), 7.26 (m, 2 H), 7.01 (m, 4 H), 3.76 (s, 2 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 164.4 (d, $J_{F,C}$ = 121.8 Hz), 163.3, 161.9 (d, $J_{F,C}$ = 116.9 Hz), 143.4 (d, $J_{F,C}$ = 8.5 Hz), 132.6 (d, $J_{F,C}$ = 9.2 Hz), 129.9 (d, $J_{F,C}$ = 8.2 Hz), 123.6 (d, $J_{F,C}$ = 2.5 Hz), 117.2 (d, $J_{F,C}$ = 22.3 Hz), 115.1 (d, $J_{F,C}$ = 21.6 Hz), 114.4 (d, $J_{F,C}$ = 21.6 Hz), 79.7, 67.3, 27.9 ppm. IR (KBr): $\tilde{\nu}$ = 2947, 1602, 1504, 1223, 830 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{16}F_2NO$ $[M + H]^+$ 288.1200; found 288.1201.

2-(5-Bromo-4′-nitro-[1,1′-biphenyl]-2-yl)-4,4-dimethyl-2-oxazoline (6k): 2-(4-Bromophenyl)-4,4-dimethyl-2-oxazoline (**4b**, 127.0 mg, 0.5 mmol) and 1-iodo-4-nitrobenzene (249.0 mg, 1.0 mmol) afforded **6k** (159.0 mg, 85% yield) as a brown solid; m.p. 112–114 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.19 (dt, J = 8.7, 2.4 Hz, 2 H), 7.70 (d, J = 8.3 Hz, 1 H), 7.55 (dd, J = 8.3, 2.0 Hz, 1 H), 7.46 (m, 2 H), 7.43 (t, J = 2.0 Hz, 1 H), 3.78 (s, 2 H), 1.23 (s, 6 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 162.4, 147.3, 146.4, 141.3, 133.0, 132.2, 131.6, 129.3, 123.3, 79.7, 67.6, 27.8 ppm. IR (KBr): $\tilde{\nu}$ = 2961, 2877, 1658, 1517, 1335, 1040, 858 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{16}BrN_2O_3$ $[M + H]^+$ 375.0344; found 375.0359.

Computational Methods: All the calculations were done in the Gaussian 03 suite programs,[25] and the geometries and Gibbs energies were calculated by using the B3LYP method.[22] For phenyl-2-oxazolines **6a**–**6i**, the 6-31+G(d,p) basis set was used to optimize the geometries and obtain the energetic treatment. For iodides **6j**–**6l**, the CEP-31G was used as the basis set.[26] The solvent system effects were evaluated by using the polarized continuum model (PCM)[27] with the default parameters for THF. To obtain the pK_a values for all of the molecules, the deprotonated molecules were also optimized in the same models. The pK_a values were then calculated by means of the isodesmic reactions using the appropriate heterocycle with an experimental pK_a value as described in the reaction: Het–H + $R^- \rightarrow$ RH + Het^-.[21]

These approaches have been described recently, and the results are important to describe the experimental results obtained from syntheses that involve heterocyclic compounds and C–H activation. The reference compound used in our studies was pyridine, and we followed the method described in the literature.[21]

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all synthesized compounds and experimental details of the computational thermochemistry study.

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[1] For representative reviews, see: a) J. A. Frump, *Chem. Rev.* **1971**, *71*, 483–505; b) A. I. Meyers, M. Reuman, *Tetrahedron* **1985**, *41*, 837–860; c) A. I. Meyers, T. G. Gant, *Tetrahedron* **1994**, *50*, 2297–2360.

[2] N. Zhang, T. Pompe, I. Amin, R. Luxenhofer, C. Werner, R. Jordan, *Macromol. Biosci.* **2012**, *12*, 926–936.

[3] A. Bolomolova, S. K. Filippov, L. A. Starovoytova, K. P. Borislav, O. Sedlacek, M. Hruby, P. Stepanek, *J. Phys. Chem. B* **2014**, *118*, 4940–4950.

[4] A. Schulz, S. Jaksch, R. Schubel, E. Wegener, Z. Di, Y. Han, A. Meister, J. Kressler, A. V. Kabanov, R. Luxenhofer, *ACS Nano* **2014**, *8*, 2686–2696.

[5] a) S. Y. Jeong, Q. P. B. Nguyen, H. J. Kim, T. H. Kim, *Bull. Korean Chem. Soc.* **2011**, *32*, 4133–4136; b) L. Chen, X. Ding, L. Gong, E. Meggers, *Dalton Trans.* **2013**, *42*, 5623–5626.

[6] a) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; b) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; c) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345; d) G.-J. Lee, T. Kim, J. N. Kim, U. Lee, *Tetrahedron: Asymmetry* **2002**, *13*, 9–12; e) G. C. Hargaden, P. J. Guiry, *Chem. Rev.* **2009**, *109*, 2505–2550; f) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.

[7] B. M. Degnan, C. J. Hawkins, M. F. Lavin, E. J. McCaffrey, D. L. Parry, A. L. van den Brenk, D. J. Watterst, *J. Med. Chem.* **1989**, *32*, 1349–1354.

[8] L. Mander, H.-W. Liu, *Comprehensive Natural Products II: Chemistry and Biology*, Elsevier Ltd., Oxford, UK, **2010**, vol. 1, p. 539–541.

[9] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933; b) M. Yus, F. Foubelo, in: *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, Germany, **2005**, vol. 1; c) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802–3824; *Angew. Chem.* **2007**, *119*, 3876; d) M. C. Whisler, S. MacNeil, P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225; *Angew. Chem.* **2004**, *116*, 2256; e) M. Zenzola, L. Degennaro, P. Trinchera, L. Carroccia, A. Giovine, G. Romanazzi, P. Mastrorilli, R. Rizzi, L. Pisano, R. Luisi, *Chem. Eur. J.* **2014**, *20*, 12190–12200.

[10] a) T. G. Gant, A. I. Meyers, *Tetrahedron* **1994**, *50*, 2297–2360; b) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356–363; c) S. E. Hagen, J. M. Domaglia, *J. Heterocycl. Chem.* **1990**, *27*, 1609–1616; d) A. I. Meyers, W. B. Avila, *Tetrahedron Lett.* **1980**, *21*, 3335–3358; e) A. I. Meyers, W. B. Avilla, *J. Org. Chem.* **1981**, *46*, 3881–3886; f) M. Reuman, A. I. Meyers, *Tetrahedron* **1985**, *41*, 837–860; g) J. Mortier, *Curr. Org. Chem.* **2011**, *15*, 2413–2447; h) N. Robert, T. Martin, J. Grisel, J. Lazaar, C. Hoarau, F. Marsais, *Tetrahedron Lett.* **2009**, *50*, 1768–1770; i) N. Robert, A.-L. Bonneau, C. Hoarau, F. Marsais, *Org. Lett.* **2006**, *8*, 6071–6074; j) A. I. Meyers, J. Willemsen, *Tetrahedron* **1998**, *54*, 10493–10511; k) A. I. Meyers, R. A. Gabel, *Heterocycles* **1978**, *11*, 133–138; l) A. I. Meyers, E. D. Michelich, *J. Am. Chem. Soc.* **1975**, *97*, 7383–7385.

[11] a) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539–3540; b) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514–8515; c) M. Uchiyama, H. Naka, Y. Matsumoto, T. Ohwada, *J. Am. Chem. Soc.* **2004**, *126*, 10526–10527; d) H. Naka, M. Uchiyama, Y. Matsumoto, A. E. Y. Wheatley, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc.* **2007**, *129*, 1921–1930; e) J. M. L'Helgoual'ch, G. Bentabed-Ababsa, F. Chevallier, M. Yonehara, M. Uchiyama, A. Derdour, F. Mongin, *Chem. Commun.* **2008**, *42*, 5375–5377.

[12] E. Bellamy, O. Bayh, C. Hoarau, F. Trécourt, G. Quéguiner, F. Marsais, *Chem. Commun.* **2010**, *46*, 7043–7045.

[13] M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Y. Kajihara, T. Miyoshi, T. Sakamoto, K. Yoshinori, K. Morokuma, *J. Am. Chem. Soc.* **2008**, *130*, 472–480.

[14] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681–7684; *Angew. Chem.* **2007**, *119*, 7825; b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503–1507; *Angew. Chem.* **2008**, *120*, 1526; c) Z. Dong, G. C. Clososki, S. H. Wunderlich, A. Unsinn, J. S. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 457–468; d) T. Noji, H. Fujiwara, K. Okano, H. Tokuyama, *Org. Lett.* **2013**, *15*, 1946–1949; e) T. Klatt, D. S. Roman, T. León, P. Knochel, *Org. Lett.* **2014**, *16*, 1232–1235; f) S. Duez, A. K. Steib, P. Knochel, *Org. Lett.* **2012**, *14*, 1951–1953; g) D. Haas, M. Mosrin, P. Knochel, *Org. Lett.* **2013**, *15*, 6162–6165; h) A. Unsinn, S. H. Wunderlich, A. Jana, K. Karaghiosof, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 14687–14696; i) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794–9824; *Angew. Chem.* **2011**, *123*, 9968; j) T. Klatt, J. T. Markiewicz, C. Samann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253–4269; k) A. Unsinn, C. J. Rohbogner, P. Knochel, *Adv. Synth. Catal.* **2013**, *355*, 1553–1560; l) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958–2961; *Angew. Chem.* **2006**, *118*, 3024–3027.

[15] K. Schwekendiek, F. Glorius, *Synthesis* **2006**, *18*, 2996–3002.

[16] R. G. Harvey, C. Cortez, *Tetrahedron* **1997**, *53*, 7101–7118.

[17] a) A. G. De Crisci, K. L. Chung, A. G. Solis-Ibarra, R. M. Waymouth, *Organometallics* **2013**, *32*, 2257–2266; b) J. Yi, X. Lu, Y.-Y. Sun, B. Xião, L. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12409–12413; *Angew. Chem.* **2013**, *125*, 12635; c) G. Peng, X. Quin, S. Min, *Synlett* **2013**, *24*, 1255–1259; d) J. T. Binder, C. J. Cordier, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 17003–17006; e) L. Xufing, S. Jian, X. Yanyan, L. Delain, *Organometallics* **2011**, *30*, 3284–3292; f) M. F. Z. J. Amaral, L. A. Deliberto, C. R. Souza, R. M. Z. G. Naal, Z. Naal, G. C. Clososki, *Tetrahedron* **2014**, *70*, 3249–3258.

[18] a) T.-L. Rathman, W. F. Bailey, *Org. Process Res. Dev.* **2009**, *13*, 144–151; b) P. D. Pansegrau, W. F. Rieker, A. I. Meyers, *J. Am. Chem. Soc.* **1988**, *110*, 7178–7184; c) A. I. Meyers, P. D. Pansegrau, *J. Chem. Soc., Chem. Commun.* **1985**, 690–691; d) A. I. Meyers, P. D. Pansegrau, *Tetrahedron Lett.* **1983**, *24*, 4935–4938.

[19] a) J. Ho, M. L. Coote, M. Franco-Pérez, R. Gómez-Balderas, *J. Phys. Chem. A* **2010**, *114*, 11992–12003; b) J. Ho, M. L. Coote, *Theor. Chem. Acc.* **2010**, *125*, 3–21.

[20] a) I. Hyla-Kryspin, S. Grimme, H. H. Büker, N. M. M. Nibbering, F. Cottet, M. Schlosser, *Chem. Eur. J.* **2005**, *11*, 1251–1256; b) M. Schlosser, E. Marzi, F. Cottet, B. H. Heinz, N. M. M. Nibbering, *Chem. Eur. J.* **2001**, *7*, 3511–3516; c) M. Schlosser, F. Mongin, J. Porwisiak, W. Dmowski, H. H. Büker, N. M. M. Nibbering, *Chem. Eur. J.* **1998**, *4*, 1281–1286; d) H. H. Büker, N. M. M. Nibbering, D. Espinosa, F. Mongin, M. Schlosser, *Tetrahedron Lett.* **1997**, *38*, 8519–8522.

[21] a) K. Snégaroff, T. T. Nguyen, N. Marquise, Y. S. Halauko, P. J. Harford, T. Roisnel, V. E. Matulis, O. A. Ivanshkevisch, F. Chevallier, A. E. H. Wheatley, P. C. Gros, F. Mongin, *Chem. Eur. J.* **2011**, *17*, 13284–13297; b) R. R. Kadiyala, D. Tilly, E. Nagaradja, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, Y. S. Halauko, F. Chevallier, P. C. Gros, F. Mongin, *Chem. Eur. J.* **2013**, *19*, 7944–7960; c) F. Chevallier, Y. S. Halauko, C. Pecceu, I. F. Nassar, T. U. Dam, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Mongin, *Org. Biomol. Chem.* **2011**, *9*, 4671–4684; d) F. Chevallier, T. Blin, E. Nagaradja, F. Lassagne, T. Roisnel, Y. S. Halauko, V. E. Matulis, O. A. Ivashkevich, F. Mongin, *Org. Biomol. Chem.* **2012**, *10*, 4878–4885; e) S. Y. Halauko, V. E. Matulis, O. A. Ivashkevich, Y. V. Grigoriev, P. N. Gaponik, *Tetrahedron* **2010**, *66*, 3415–3420; f) A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928–7932.

[22] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789; c) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.

[23] a) P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079–8081; *Angew. Chem.* **2008**, *120*, 8199; b) D. R. Armstrong, P. García-Álvarez, A. R. Kennedy, R. E. Mulvey, J. A. Parkinson, *Angew. Chem. Int. Ed.* **2010**, *49*, 3185–3188; *Angew. Chem.* **2010**, *122*, 3253.

[24] D. D. Perrin, W. L. F. Amarego, *Purification of Laboratory Chemicals*, Pergamon, Oxford, UK, **1988**.

[25] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R.

Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. W. M. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, revision C.02, Gaussian, Inc., Wallingford CT, **2004**.

[26] W. J. Stevens, M. Krauss, H. Basch, P. G. Jasien, *Can. J. Chem.* **1992**, *70*, 612–630.

[27] J. Tomasi, M. Persico, *Chem. Rev.* **1994**, *94*, 2027–2094.

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