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A convenient synthesis of 4-substituted 3-ethoxy-5-methylisoxazoles by palladium-catalyzed coupling reactions

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Abstract—The coupling reactions were performed using 3-ethoxy-4-iodo-5-methylisoxazole (**4**) as the key intermediate. Coupling of **4** under Suzuki–Miyaura or Stille conditions using $Pd(PPh_3)_2Cl_2$ and arylboronic acids or aryltin analogues, respectively, gave 4-aryl substituted isoxazoles in yields ranging from 49% for the 3-pyridyl analogue **14**, to 96% for the 4-pyridyl analogue **12**. Under Heck reaction conditions using $Pd(PPh_3)_2Cl_2$ and **4**, analogues of 3-ethoxy-5-methylisoxazole containing vinylic or acetylenic groups in the 4-position were synthesized in yields ranging from 58 to 98%. 3-Ethoxy-5-methylisoxazol-4-ylmagnesium bromide (**19**), prepared from **4** and isopropylmagnesium bromide, reacted smoothly with benzaldehyde or benzoyl chloride to give the desired 4-[hydroxy(phenyl)methyl] analogue **21** and 4-benzoyl-3-ethoxy-5-methylisoxazole (**22**), respectively. Transmetallation of **19** with $ZnCl_2$ and subsequent treatment with $Pd(PPh_3)_2Cl_2$ and 4-iodotoluene gave 3-ethoxy-5-methyl-4-(4-methylphenyl)isoxazole (**23**) in 80% yield.

1. Introduction

The central excitatory neurotransmitter (*S*)-glutamic acid (Glu) operates through ionotropic Glu receptors (iGluRs), subdivided into *N*-methyl-D-aspartic acid (NMDA), (*RS*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA), and kainic acid receptors, as well as metabotropic Glu receptors (mGluRs) of which eight receptor subtypes are known.[1–3] All of these receptors are potential therapeutic targets, and the first step in the development of Glu receptor subtype-selective drugs on a rational basis is the design of subtype-selective receptor ligands (Fig. 1).

Analogues of (*S*)-AMPA (**1**) containing different alkyl or, in particular, aryl and heteroaryl substituents in the 5-position of the 3-isoxazolol ring have played a key role in the development of the pharmacology of the AMPA-receptor.[4–6] In contrast to (*S*)-AMPA (**1**), the isomeric 3-isoxazolol amino acid (*S*)-2-amino-3-(3-hydroxy-4-methylisoxazol-5-yl)propionic acid [(*S*)-4-Me-homoibotenic acid (**2**)] interacts with AMPA receptors as well as with mGluR subtypes.[7] Replacement of the methyl group of **2** with more bulky nonaromatic substituents has been shown to enhance the selectivity of these analogues for mGluRs.[7,8] In light of these observations and the results of structure–activity studies on 5-aryl substituted analogues of (*S*)-AMPA (**1**), we decided to develop a method for the synthesis of analogues of **2** containing aryl or heteroaryl substituents in the 4-position of the 3-isoxazolol ring.

The classical method of synthesizing 4,5-disubstituted 3-isoxazolols is based on reaction of hydroxylamine with appropriately substituted β-ketoesters, but these reactions inherently provide 3-isoxazolols as well as the isomeric 3-isoxazolin-5-ones in ratios dependent on the structures of the β-ketoesters and the reaction conditions.[9,10] Recently, a method for the synthesis of 3-isoxazolols without formation of 3-isoxazolin-5-ones, based on reaction of 5-acylated Meldrum's acids with *O*,*N*-diprotected hydroxylamine, was reported,[11] but none of these methods have

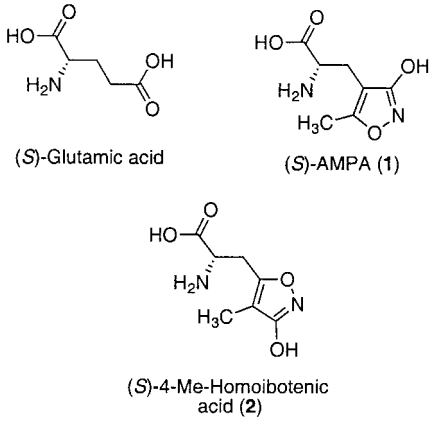

Figure 1.

Keywords: 3-hydroxy-5-methylisoxazole; cross-coupling; palladium catalyzed; Stille; Suzuki–Miyaura; Heck.

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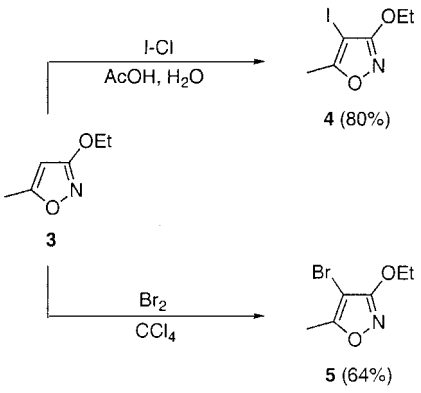


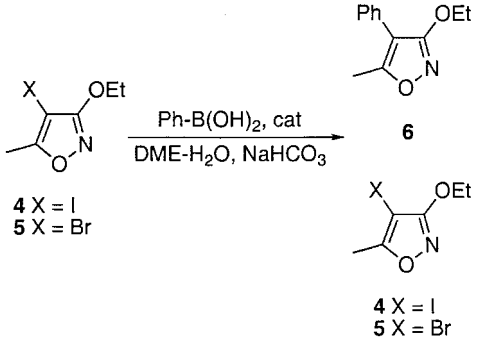
Scheme 1.

proved useful for the synthesis of 3-isoxazolols linked directly to aryl or heteroaryl ring systems in the 4-position. In the light of these synthetic limitations, we have been working on the development of methods and conditions for direct coupling between C-4 of *O*-protected and 5-substituted 3-isoxazolols and different aromatic or heteroaromatic rings.

Transition metal-catalyzed coupling of organometallic reagents with aryl halides or triflates has been widely used to form carbon–carbon bonds.[12–15] Palladium-catalyzed coupling reactions have been used for the formation of 4-aryl-3,5-dimethylisoxazole from 3,5-dimethyl-4-iodoisoxazole[16] and for the formation of 4-aryl-3-methylisoxazole from 4-(tributylstannyl)-3-methylisoxazole.[17] Furthermore, direct phenylation of 4-unsubstituted 3-(*p*-toluenesulfonyloxy)isoxazole using either benzene or phenyl iodide,[18] and coupling of alkynes and alkenes with 3,5-dimethyl-4-iodoisoxazole using a palladium catalyst has been reported.[19]

To our knowledge, this is the first report of palladium-catalyzed coupling reactions affording 4-aryl and 4-heteroaryl substituted 3-alkoxyisoxazoles, compounds which are suitable intermediates for the synthesis of pharmacologically interesting 3-isoxazolol-containing amino acids.

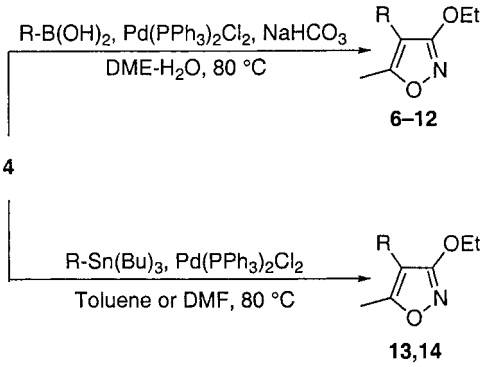
Table 1. Reactions of 4-substituted alkoxyisoxazoles using Ni- or Pd-catalysts



Starting material	X	Catalyst	**6**:**4**/**5**[a]
4	I	$Ni(PPh_3)_2Cl_2$	2:3
4	I	$Pd(PPh_3)_2Cl_2$	1:0
5	Br	$Pd(PPh_3)_2Cl_2$	1:2

[a] Product/starting material ratio as determined by NMR.

Table 2. Suzuki–Miyaura and Stille reactions of 3-ethoxy-4-iodo-5-methylisoxazole (**4**)



R	Product	Yield (%)
Ph	**6**	84
1-Naphthyl	**7**	85
2-Naphthyl	**8**	88
2-Ph-OCH_3	**9**	80
3-Ph-OCH_3	**10**	76
4-Ph-OCH_3	**11**	90
4-Pyridyl	**12**	96
2-Pyridyl	**13**	92
3-Pyridyl	**14**	49

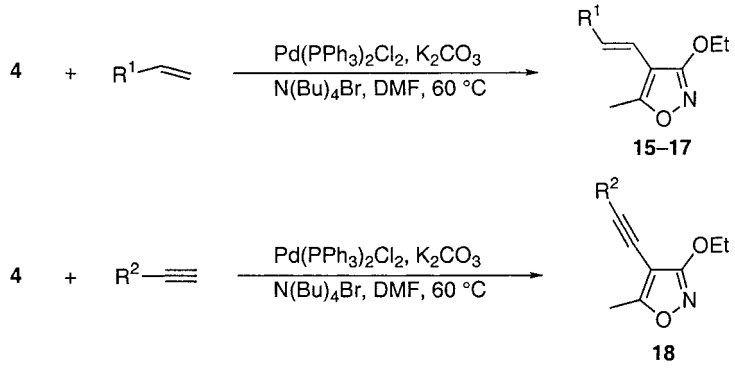
2. Results and discussion

3-Ethoxy-5-methylisoxazole (**3**)[20] was converted into **4**, in 80% yield, by treatment with iodine chloride in aqueous acetic acid and into **5**, in 64% yield, by treatment with bromine in CCl_4 (Scheme 1). Suzuki–Miyaura coupling reactions between phenylboronic acid and **4** or **5** gave 3-ethoxy-5-methyl-4-phenylisoxazole (**6**), in 84 and 33% isolated yields, respectively (Table 1, entries 2 and 3), the former reaction showing complete conversion of starting material after 18 h. Starting out with **4**, but substituting $Ni(PPh_3)_2Cl_2$ for $Pd(PPh_3)_2Cl_2$ under identical conditions only gave 40% conversion of **4** (Table 1, entry 1). Although the oxidation state of the palladium at the moment of the reaction is not entirely clear,[12,21–24] the coupling reactions described here were performed using $Pd(PPh_3)_2Cl_2$ without the addition of any kind of reducing agents or addition of triphenylphosphine, in agreement with the Suzuki–Beletskaya procedure.[22,23]

The Suzuki–Miyaura coupling reactions between **4** and the boronic acid reagents were performed in a mixture of DME and water using $NaHCO_3$ as base (Table 2). The Stille coupling reactions between **4** and the tributyltin reagents were performed in toluene or DMF (Table 2). In order to overcome problems with the separation of product from tributylstannyl halide, the products were isolated via formation of the hydrobromide salts.

The palladium-catalyzed Heck reactions have been extensively used for arylation and vinylation of olefins.[25,26] The reactions shown in Table 3 were performed under conditions

Table 3. Heck reaction of 3-ethoxy-4-iodo-5-methylisoxazole (**4**)



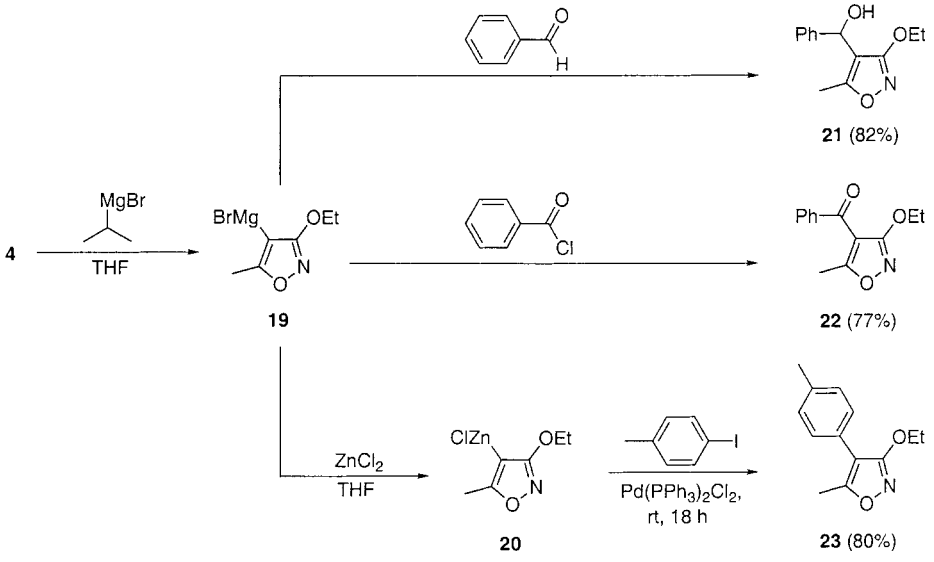
R^1	R^2	Product	Yield (%)
Ph	–	**15**	91
CN	–	**16**	77
$COOCH_3$	–	**17**	98
–	Ph	**18**	58

described by Jeffery,[27,28] using DMF as solvent, tetrabutylammonium bromide as the phase transfer reagent, and K_2CO_3 as base.

In Scheme 2, the incorporation of different functionalities into the 4-position of compound **3** via metallation of this position is outlined. In agreement with previous findings,[29] reactions of **3** with alkyllithium reagents primarily resulted in deprotonation of the methyl group of the 5-position of **3**. Recently, iodine/magnesium exchange reactions between alkylmagnesium halides and aryl iodides have been reported for effective generation of arylmagnesium halides.[30–36] Thus, compound **4** was effectively converted into the Grignard intermediate **19**, which was transmetallated with $ZnCl_2$ to give **20**, and subsequent palladium-catalyzed reaction of **20** with 4-iodotoluene gave **23** in good yield. The heteroarylmagnesium bromide **19** was smoothly converted into **21** and **22** by reaction with benzaldehyde and benzoyl chloride, respectively (Scheme 2).

In conclusion, different palladium-catalyzed coupling reactions have been effectively used for the incorporation of aromatic, heteroaromatic, and vinylic or acetylenic groups into the 4-position of compound **3**. Furthermore, 4-substituted analogues of **3** have been synthesized via the Grignard intermediate **19**, formed by an iodine/magnesium exchange reaction between compound **4** and isopropylmagnesium bromide.

These results have paved the way for the synthesis of analogues of the 3-isoxazolol amino acid **2**, in which the methyl group has been replaced by different aromatic or unsaturated groups. This group of compounds are predicted to be interesting ligands for central Glu receptors.



Scheme 2.

3. Experimental

3.1. General

^{1}H and associated proton test (APT) NMR spectra were recorded on a 300 MHz Varian Gemini spectrometer, using $CDCl_3$ as the solvent. Chemical shifts are given in ppm (δ) using TMS as the internal standard, and coupling constants (J) are given in Hertz. Column chromatography (CC) was performed on Merck silica gel 60 (0.063–0.200 mm). Compounds were visualized on TLC (silica gel 60 F_{254} plates, Merck) using UV light and $KMnO_4$ spraying reagent. All reactions involving air-sensitive reagents were performed under N_2. Melting points were determined in open capillaries and are uncorrected. All solvents and reagents were obtained from Fluka, Aldrich, or Maybridge and used without further purification, except THF which was distilled from Na/benzophenone ketyl under N_2, and DMF which was stored over 3 Å molecular sieves. The anisolboronic acids,[37] 2-naphthaleneboronic acid,[38] 4-pyridineboronic acid,[39] and 2-(tributylstannyl)-pyridine[40] were prepared as previously described. A solution of $ZnCl_2$ in THF was prepared by flame-drying $ZnCl_2$ in vacuo and dissolving it in dry THF. A solution of isopropylmagnesium bromide in THF was prepared as previously described.[41] Elemental analyses were performed at Analytical Research Department, H. Lundbeck A/S, Denmark or by J. Theiner, Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna, Austria.

Accurate mass determinations (±2 ppm) were performed at the University of Southern Denmark, Odense University, Department of Chemistry, on an IonSpec Fourier Transform Mass Spectrometer, using matrix assisted laser desorption ionization (MALDI) with 2,5-dihydroxybenzoic acid as matrix.

3.1.1. 3-Ethoxy-4-iodo-5-methylisoxazole (4). To a solution of compound **3**[20] (8.0 g, 63 mmol) in AcOH (250 mL) and water (300 mL) was added iodine chloride (12.2 g, 75 mmol). The stirred solution was heated to 80°C for 2.5 h, and was cooled to rt. The solution was added to a 10% solution of Na_2SO_3 in water (50 mL) and water (250 mL), and the white precipitate was filtered off and redissolved in acetone (200 mL). Impurities were filtered off and to the filtrate was added water (800 mL) giving white crystals (12.8 g, 80%). Recrystallization (hexane) gave **4** as white crystals: mp 56.5–57.5°C, ^{1}H NMR δ 1.44 (t, J=7.2 Hz, 3H), 2.37 (s, 3H), 4.32 (q, J=7.2 Hz, 2H), ^{13}C NMR δ 12.84, 14.37, 49.42, 66.24, 170.98, 171.12. Anal. Calcd for $C_6H_8NO_2I$: C, 28.48, H, 3.19, N, 5.53. Found: C, 28.59, H, 3.19, N, 5.56.

3.1.2. 4-Bromo-3-ethoxy-5-methylisoxazole (5). To a solution of compound **3** (2.4 g, 18.9 mmol) in CCl_4 (30 mL) was added Br_2 (3.3 g, 20.8 mmol), and the reaction was left for 3 h at rt and subsequently concentrated in vacuo. CC (toluene/EtOAc 9:1, 1% AcOH) gave **5** as a brown oil (2.5 g, 64%) that turned black on standing: ^{1}H NMR δ 1.45 (t, J=7.5 Hz, 3H), 2.34 (s, 3H), 4.34 (q, J=7.5 Hz, 2H), ^{13}C NMR δ 11.75, 14.31, 66.17, 82.68, 167.51, 168.69.

3.1.3. Palladium-catalyzed Suzuki coupling of 3-ethoxy-4-iodo-5-methylisoxazole (4). *General procedure*. To a solution of compound **4** (1.0 g, 4.0 mmol) in DME (10 mL) was added $Pd(PPh_3)_2Cl_2$ (80 mg, 0.11 mmol). The stirred mixture was left at rt for 15 min followed by addition of water (10 mL), $NaHCO_3$ (1.0 g, 12.0 mmol) and the boronic acid (5.9 mmol). The reaction was stirred at 80°C overnight. The mixture was cooled to rt, and diethylether (20 mL) was added. The two phases were separated, and the organic phase was washed with water (10 mL), 2 M NaOH (2×10 mL), and water (10 mL). Drying of the organic phase ($MgSO_4$), filtration, and concentration in vacuo gave the crude product that was purified by CC.

3.1.4. 3-Ethoxy-5-methyl-4-phenylisoxazole (6). CC (hexane/EtOAc 20:1, 1% AcOH) gave **6** (84%) as white crystals: mp 46–47.5°C, ^{1}H NMR δ 1.45 (t, J=6.9 Hz, 3H), 2.45 (s, 3H), 4.40 (q, J=7.2 Hz, 2H), 7.43–7.45 (m, 5H), ^{13}C NMR δ 12.46, 14.45, 65.64, 106.87, 127.20, 128.28, 128.57, 129.12, 166.03, 169.54. Anal. Calcd for $C_{12}H_{13}O_2N$: C, 70.92, H, 6.45, N, 6.89. Found: C, 71.15, H, 6.74, N, 6.90.

3.1.5. 3-Ethoxy-4-(1-naphthyl)-5-methylisoxazole (7). CC (toluene, 1% AcOH) gave **7** (85%) as orange crystals. Recrystallization (diethylether/hexane) gave white crystals: mp 83–85°C, ^{1}H NMR δ 1.31 (t, J=7.0 Hz, 3H), 2.24 (s, 3H), 4.35 (q, J=7.0 Hz, 2H), 7.36–7.94 (m, 7H), ^{13}C NMR δ 12.14, 14.44, 65.68, 106.02, 125.44, 125.62, 126.06, 126.21, 126.24, 128.48, 128.65, 128.73, 132.16, 133.85, 167.58, 170.32. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87, H, 5.97, N, 5.53. Found: C, 75.99, H, 5.97, N, 5.57.

3.1.6. 3-Ethoxy-4-(2-naphthyl)-5-methylisoxazole (8). CC (toluene, 1% AcOH) gave **8** (88%) as orange crystals. Recrystallization (diethylether/hexane) gave white crystals: mp 39–40°C, ^{1}H NMR δ 1.39 (t, J=7.0 Hz, 3H), 2.44 (s, 3H), 4.35 (q, J=7.0 Hz, 2H), 7.48 (dd, J=8.5, 1.8 Hz, 1H), 7.40–7.45 (m, 2H), 7.75–7.84 (m, 3H), 7.80 (s, 1H), ^{13}C NMR δ 12.68, 14.57, 65.80, 107.07, 126.19, 126.32, 126.37, 126.65, 127.36, 127.74, 127.98, 128.25, 132.44, 133.45, 166.37, 169.77. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87, H, 5.97, N, 5.53. Found: C, 75.77, H, 6.05, N, 5.52.

3.1.7. 3-Ethoxy-4-(2-methoxyphenyl)-5-methylisoxazole (9). CC (toluene, 1% AcOH) gave **9** (80%) as white crystals: mp 58–59°C, ^{1}H NMR δ 1.38 (t, J=7.0 Hz, 3H), 2.27 (s, 3H), 3.82 (s, 3H), 4.33 (q, J=7.0 Hz, 2H), 6.97 (dd, J=8.0, 0.6 Hz, 1H), 7.01 (ddd, J=7.4, 7.4, 1.1 Hz, 1H), 7.25 (dd, J=7.5, 1.8 Hz, 1H), 7.34 (ddd, J=8.0, 7.4, 1.8 Hz, 1H), ^{13}C NMR δ 12.70, 14.53, 55.32, 65.45, 103.57, 111,19, 117.67, 120.57, 129.33, 131.53, 157.14, 167.47, 170.03. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94, H, 6.48, N, 6.00. Found C, 67.18, H, 6.52, N, 5.95.

3.1.8. 3-Ethoxy-4-(3-methoxyphenyl)-5-methylisoxazole (10). CC (toluene, 1% AcOH) gave **10** (76%) as a yellow oil: ^{1}H NMR δ 1.44 (t, J=6.9 Hz, 3H), 2.54 (s, 3H), 3.84 (s, 3H), 4.37 (q, J=7.2 Hz, 2H), 6.87 (ddd, J=8.4, 2.7, 1.2 Hz, 1H), 7.00–7.03 (m, 2H), 7.34 (dd, J=8.1, 8.1 Hz, 1H), ^{13}C NMR δ 12.68, 14.56, 55.17, 65.73, 106.82, 112.61, 114.20, 120.72, 129.67, 130.51, 159.77, 166.25, 169.60. HRMS (MALDI): $C_{13}H_{15}NO_3$ requires $[M+H]^+$ at m/z 234.1125, found 234.1127.

3.1.9. 3-Ethoxy-4-(4-methoxyphenyl)-5-methylisoxazole (11). CC (toluene, 1% AcOH) gave **11** (90%) as orange crystals. Recrystallization (hexane) gave yellow crystals: mp 38–39°C, ^{1}H NMR δ 1.43 (t, J=7.0 Hz, 3H), 2.42 (s, 3H), 3.84 (s, 3H), 4.37 (q, J=7.0 Hz, 2H,), 6.97 (d, J=8.8 Hz, 2H), 7.35 (d, J=8.8 Hz, 2H), ^{13}C NMR δ 12.49, 14.56, 55.23, 65.64, 106.59, 114.14, 121.45, 129.59, 158.89, 165.45, 169.70. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94, H, 6.48, N, 6.00. Found: C, 66.74, H, 6.32, N, 5.94.

3.1.10. 3-Ethoxy-5-methyl-4-(4-pyridyl)isoxazole (12). CC (toluene, 1% AcOH) gave **12** (96%) as white crystals. Recrystallization (diethylether/hexane) gave white crystals: mp 90–91°C, ^{1}H NMR δ 1.47 (t, J=7.1 Hz, 3H), 2.53 (s, 3H), 4.40 (q, J=7.1 Hz, 2H), 7.41 (dd, J=4.5, 1.6 Hz, 2H), 8.64 (dd, J=4.6, 1.5 Hz, 2H), ^{13}C NMR δ 12.99, 14.37, 65.95, 104.54, 122.07, 137.19, 150.04, 167.67, 169.20. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69, H, 5.92, N, 13.72. Found: C, 64.75, H, 6.07, N, 13.63.

3.1.11. Palladium-catalyzed Stille coupling of 3-ethoxy-4-iodo-5-methylisoxazole (4); 3-ethoxy-5-methyl-4-(2-pyridyl)isoxazole (13). To a solution of compound **4** (3.0 g, 11.9 mmol) in toluene (50 mL) was added $Pd(PPh_3)_2Cl_2$ (164 mg, 0.23 mmol), and the mixture was left at rt for 15 min. 2-(Tributylstannyl)pyridine (6.3 g, 17.1 mmol) was added, and the reaction was left at 80°C for 16 h. The solution was concentrated in vacuo followed by CC (toluene, 1% AcOH). The resulting crystals were dissolved in EtOAc (30 mL) and cooled on ice. 33% HBr in AcOH (3 mL) was added dropwise, and the white precipitate was filtered of and washed with EtOAc, dried and added to water (50 mL). The aqueous suspension was neutralized using saturated $NaHCO_3$ (25 mL) to neutral pH and was extracted with EtOAc (3×50 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo to give yellow crystals (2.4 g, 92%). Recrystallization (heptane) gave **13** as white crystals: mp 48–49°C, ^{1}H NMR δ 1.49 (t, J=7.2 Hz, 3H), 2.71 (s, 3H), 4.44 (q, J=7.2 Hz, 2H), 7.15 (dd, J=7.4, 5.0 Hz, 1H), 7.70 (dd, J=7.4, 7.4 Hz, 1H), 7.75 (d, J=8.0 Hz, 1H), 8.61 (d, J=4.9 Hz, 1H), ^{13}C NMR δ 13.81, 14.58, 65.90, 105.97, 121.40, 122.09, 136.31, 149.38, 150.02, 169.39, 170.24. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69, H, 5.92, N, 13.72. Found: C, 64.78, H, 5.92, N, 13.72.

3.1.12. 3-Ethoxy-5-methyl-4-(3-pyridyl)isoxazole (14). To a solution of compound **4** (3.0 g, 11.9 mmol) in DMF (50 mL), was added $Pd(PPh_3)_2Cl_2$ (164 mg, 0.23 mmol), and the solution was left at rt for 15 min. 3-(Tributylstannyl)pyridine (6.3 g, 17.1 mmol) was added, and the reaction mixture was left at 80°C for 16 h. Workup as described above for compound **13**. Yield: 49% as white crystals. Recrystallization (hexane) gave **14** as white crystals: mp 81–82°C, ^{1}H NMR δ 1.45 (t, J=7.2 Hz, 3H), 2.50 (s, 3H), 4.40 (q, J=6.9 Hz, 2H), 7.44 (dd, J=8.1, 4.8 Hz, 1H), 7.86 (ddd, J=8.1, 2.1, 1.8 Hz, 1H), 8.58 (d, J=3.9 Hz, 1H), 8.72 (bs, 2H), ^{13}C NMR δ 12.74, 14.49, 66.08, 103.66, 123.92, 126.10, 136.33, 147.18, 147.90, 167.05, 169.36. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69, H, 5.92, N, 13.72. Found: C, 64.80, H, 5.94, N, 13.54.

3.1.13. Palladium-catalyzed Heck coupling of 3-ethoxy-4-iodo-5-methylisoxazole (4) with vinylic compounds. *General procedure*. A stirred mixture of **4** (1.0 g, 4.0 mmol), the vinylic compound (7.9 mmol), $N(Bu)_4Br$ (1.3 g, 4.0 mmol), K_2CO_3 (1.4 g, 9.9 mmol) and $Pd(PPh_3)_2Cl_2$ (55 mg, 0.08 mmol) in DMF (10 mL) was heated for 16 h at 60°C followed by filtration and concentration in vacuo. The black oil was redissolved in diethylether (40 mL) and water (40 mL), and the organic phase was washed twice with water. Drying of the organic phase ($MgSO_4$), filtration and concentration in vacuo gave the crude product that was purified by CC.

3.1.14. 3-Ethoxy-5-methyl-4-*trans*-styrylisoxazole (15). CC (toluene, 1% AcOH) gave **15** (91%) as slightly orange crystals. Recrystallization (hexane) gave white crystals: mp 79.5–80.5°C, ^{1}H NMR δ 1.49 (t, J=7.0 Hz, 3H), 2.41 (s, 3H), 4.39 (q, J=7.1 Hz, 2H), 6.67 (d, J=16.5 Hz, 1H), 7.13 (d, J=16.6 Hz, 1H), 7.24 (dd, J=7.3, 7.3 Hz, 1H), 7.34 (dd, J=7.7, 7.1 Hz, 2H), 7.45 (d, J=7.4 Hz, 2H), ^{13}C NMR δ 11.93, 14.58, 65.79, 104.73, 114.87, 126.14, 127.54, 128.68, 129.52, 137.61, 166.48, 169.90. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34, H, 6.59, N, 6.11. Found: C, 73.12, H, 6.50, N, 6.06.

3.1.15. *trans*-3-(3-Ethoxy-5-methylisoxazol-4-yl)acrylonitrile (16). CC (toluene, 1% AcOH) gave **16** (77%) as yellow crystals. Recrystallization (diethylether) gave white crystals: mp 111–111.5°C, ^{1}H NMR δ 1.46 (t, J=7.0 Hz, 3H), 2.42 (s, 3H), 4.37 (q, J=7.0 Hz, 2H), 6.00 (d, J=16.5 Hz, 1H), 7.05 (d, J=16.5 Hz, 1H), ^{13}C NMR δ 11.78, 14.39, 66.48, 96.31, 103.47, 118.39, 136.70, 169.43, 170.61. Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66, H, 5.66, N, 15.72. Found: C, 60.85, H, 5.76, N, 15.81.

3.1.16. Methyl *trans*-3-(3-ethoxy-5-methylisoxazol-4-yl)-acrylate (17). CC (toluene, 1% AcOH) gave **17** as orange crystals (98%). Recrystallization (diethylether/hexane) gave slightly orange crystals: mp 54.5–55.0°C, ^{1}H NMR δ 1.47 (t, J=7.0 Hz, 3H), 2.44 (s, 3H), 3.79 (s, 3H), 4.37 (q, J=7.0 Hz, 2H), 6.50 (d, J=15.9 Hz, 1H), 7.37 (d, J=15.9 Hz, 1H), ^{13}C NMR δ 11.92, 14.50, 51.58, 66.19, 103.59, 117.85, 131.09, 167.81, 169.84, 170.63. Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86, H, 6.20, N, 6.63. Found: C, 56.80, H, 6.10, N, 6.45.

3.1.17. 3-Ethoxy-5-methyl-4-(phenylethynyl)isoxazole (18). A stirred mixture of **4** (1.0 g, 4.0 mmol), phenylacetylene (880 μL, 8.0 mmol), $N(Bu)_4Br$ (1.3 g, 4.0 mmol), K_2CO_3 (1.4 g, 9.9 mmol) and $Pd(PPh_3)_2Cl_2$ (55 mg, 0.08 mmol) in DMF (10 mL) was heated for 16 h at 60°C followed by filtration and concentration in vacuo. The black oil was redissolved in diethylether (40 mL) and water (40 mL) and the organic phase was washed twice with water. Drying of the organic phase ($MgSO_4$), filtration, and concentration in vacuo followed by CC (hexane/EtOAc 5:1, 1% AcOH) gave **18** (530 mg, 58%) as a colourless oil: ^{1}H NMR δ 1.46 (t, J=7.0 Hz, 3H), 2.44 (s, 3H), 4.35 (q, J=7.0 Hz, 2H), 7.32–7.35 (m, 3H), 7.50–7.53 (m, 2H), ^{13}C NMR δ 12.45, 14.38, 66.14, 75.83, 92.43, 94.27, 122.81, 128.35, 128.53, 131.62, 170.40, 172.64. HRMS (MALDI): $C_{14}H_{13}NO_2$ requires $[M+Na]^+$ at m/z 250.0839, found 250.0838.

3.1.18. (*RS*)-3-Ethoxy-4-[hydroxy(phenyl)methyl]-5-methylisoxazole (21). To a solution of compound **4**

(1.0 g, 4.0 mmol) in THF (20 mL), cooled to −30°C, was dropwise added 2.0 M isopropylmagnesium bromide in THF (2.5 mL, 4.9 mmol). The reaction mixture was heated to 0°C and left for 1 h followed by addition of benzaldehyde (400 μL, 4.0 mmol). The reaction was heated to rt and left overnight followed by addition of a saturated solution of NH_4Cl in water (20 mL). The organic phase was washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo. CC (toluene, 1% AcOH) gave **21** as white crystals (760 mg, 82%). Recrystallization (diethylether/hexane) gave white crystals: mp 79.5–81°C, ^{1}H NMR δ 1.35 (t, J=7.0 Hz, 3H), 2.12 (s, 3H), 3.03 (d, J=4.8 Hz, 1H), 4.25 (q, J=7.0 Hz, 2H), 5.68 (d, J=4.7 Hz, 1H), 7.27–7.39 (m, 5H), ^{13}C NMR δ 11.98, 14.40, 65.68, 66.34, 107.67, 125.87, 127.61, 128.38, 141.97, 166.92, 169.76. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94, H, 6.48, N, 6.00. Found: C, 66.80, H, 6.45, N, 5.93.

3.1.19. 4-Benzoyl-3-ethoxy-5-methylisoxazole (22). To a solution of compound **4** (2.0 g, 7.9 mmol) in THF (40 mL), cooled to −30°C, was dropwise added 2.0 M isopropylmagnesium bromide in THF (5.0 mL, 9.9 mmol). The reaction mixture was heated to 0°C and left for 1 h followed by addition of benzoyl chloride (4 mL). The reaction was heated to rt and left for 4 h followed by addition of a saturated solution of NH_4Cl in water (40 mL). The organic phase was washed with water, dried ($MgSO_4$), filtered and concentrated in vacuo. CC (toluene, 1% AcOH) gave **22** as white crystals (1.4 g, 77%). Recrystallization (hexane) gave white crystals: mp 59–60°C, ^{1}H NMR δ 1.28 (t, J=7.1 Hz, 3H), 2.50 (s, 3H), 4.30 (q, J=7.1 Hz, 2H), 7.46 (dd, J=7.1, 7.1 Hz, 2H), 7.59 (dd, J=7.1, 7.1 Hz, 1H), 7.79 (d, J=7.1 Hz, 2H), ^{13}C NMR δ 13.58, 14.18, 66.12, 107.91, 128.13, 129.38, 133.10, 137.76, 168.62, 175.99, 188.70. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52, H, 5.67, N, 6.06. Found: C, 67.39, H, 5.67, N, 6.02.

3.1.20. 3-Ethoxy-5-methyl-4-(4-methylphenyl)isoxazole (23). To a solution of compound **4** (0.45 g, 1.8 mmol) in THF (10 mL), cooled to −30°C, was dropwise added 1.5 M isopropylmagnesium bromide in THF (1.5 mL, 2.2 mmol). The reaction mixture was heated to 0°C and left for 1 h followed by addition of $ZnCl_2$ (340 mg, 2.5 mmol) in THF (5 ml). The reaction was heated to rt and left for an additional hour. 4-Iodotoluene (1.3 g, 6.0 mmol) and $Pd(PPh_3)_2Cl_2$ (40 mg, 0.06 mmol) were added and the reaction mixture was left overnight. A saturated solution of NH_4Cl in water (20 mL) was added, and the organic phase was washed with water, dried ($MgSO_4$), filtrated, and concentrated in vacuo. CC (toluene, 1% AcOH) gave **23** as yellow crystals (310 mg, 80%). Recrystallization (heptane) gave white crystals: mp: 61.5–62°C, ^{1}H NMR δ 1.43 (t, J=7.2 Hz, 3H), 2.38 (s, 3H), 2.43 (s, 3H), 4.36 (q, J=7.1 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.2 Hz, 2H), ^{13}C NMR δ 12.52, 14.54, 21.09, 65.55, 106.87, 126.17, 128.27, 129.37, 137.11, 165.79, 169.72. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87, H, 6.96, N, 6.45. Found: C, 71.70, H, 6.99, N, 6.41.

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