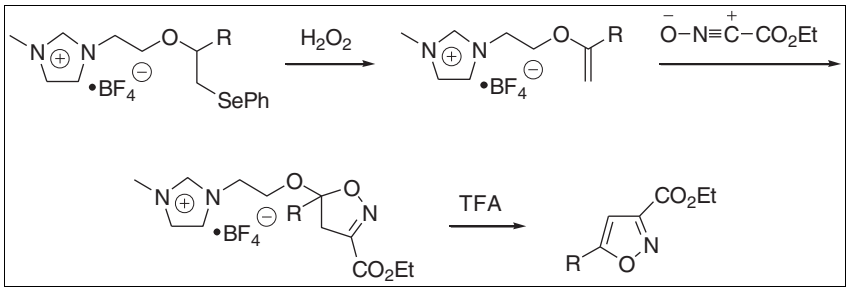
Synthesis of Ethyl Isoxazole-3-Carboxylates Using an Ionic Liquid as a Soluble Support

Shouri Sheng,[a]* Wusheng Sheng,[a] Qiaosheng Hu,[b] Hongen Qu,[b] and Mingzhong Cai[a]

[a]Institutes of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi, 330022, People's Republic of China
[b]College of Chemistry and Life Science, Gannan Normal University, Ganzhou, Jiangxi, 341000, People's Republic of China
*E-mail: shengsr@jxnu.edu.cn

Received August 31, 2011
DOI 10.1002/jhet.1673
Published online 4 November 2013 in Wiley Online Library (wileyonlinelibrary.com).



A regioselective 1,3-dipolar cycloadditions of ionic liquid-supported vinyl ethers, derived from ionic liquid-supported α-phenylselenomethyl ether, with ethyl cyanoformate *N*-oxide gave supported isoxazoline derivatives, which were then cleaved from the ionic liquid support under mild acidic conditions to afford ethyl isoxazole-3-carboxylates. This new synthetic method is simple and efficient and the products are obtained in good yields.

J. Heterocyclic Chem., **51**, 315 (2014).

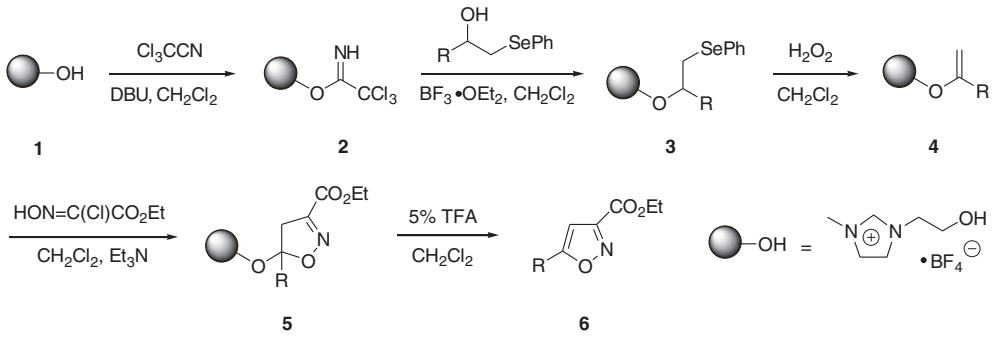
INTRODUCTION

Functionalized isoxazoles are present in a variety of natural products and represent useful synthetic building blocks [1]. They have shown considerable antimicrobial, antifungal, and herbicide activity [2]. The isoxazole moiety is present in sulfonamide antibiotics (sulfisoxazoles, oxacillin, cloxacillin, and dicloxacillin) [3], anti-rheumatic and anti-arthritic agents (leflunomide) [3], anti-inflammatory agents (isoxicam) [4], and anti-leprous agents and it is also present in a monoaminoxidase inhibitor used in psychotherapy [3]. Such a spectrum of biological activity has attracted considerable attention to these compounds, and recently, researchers have reported several solid-phase organic synthesis (SPOS) approaches using insoluble solid supports such as cross-linked polystyrene resins toward isoxazoles, including the condensation of 1,3-dicarbonyl compounds with hydroxylamine [5], the addition of nitrile oxides to the supported alkynes [6] or alkenes [7], the anchoring of nitrile oxide precursor onto the solid phase [8], or using polymer-supported selenium reagents [9]. In the field of combinatorial chemistry, although SPOS has been accepted as an efficient method to build small molecule libraries to accelerate lead generation and lead optimization [10], SPOS still exhibits several shortcomings due to the nature of the heterogeneous reaction and difficulties in reaction monitoring. Liquid-phase organic synthesis (LPOS) approaches using soluble polymer supports such as non-cross-linked polystyrene and poly(ethylene glycol) (PEG) in combinatorial synthetic methodologies facilitate the library synthesis and supersede the difficulties usually encountered during the solid-phase reactions [11]. However, the main limitation of soluble polymer supports is low loading capacity. So, the idea of searching for alternative soluble supports for high-throughput organic synthesis has been advocated. Recently, ionic liquids have been introduced as soluble supports in LPOS [12]. They have the advantages of retaining the nature of a homogeneous reaction, high loading capacity, a wide range of solvents, simple monitoring technology, and low cost. Encouraged by the aforementioned facts, and as part of our continuing effort to develop effective methods for the synthesis of substituted isoxazoles using selenium reagents [9d,13], we report here a new synthetic approach to ethyl isoxazole-3-carboxylates using an ionic liquid as a soluble support, as shown in Scheme 1. To our knowledge, this methodology has never been reported and may complement those existing in the literature.

RESULTS AND DISCUSSION

During this investigation, the β-hydroxyalkyl phenyl selenides were selected as starting materials to be anchored to ionic liquid 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([2-hydemim][BF4], **1**) via an ether bond, followed by oxidation–elimination to yield ionic liquid-supported vinyl ethers, which is based on the fact that the oxidation of phenyl selenides under extremely mild

Scheme 1. Liquid-phase organic synthesis of ethyl isoxazole-3-carboxylates.



conditions is widely employed in the formation of carbon–carbon double bonds [14]. Obviously, ionic liquid-supported α-phenylselenomethyl ether **3** derived from β-hydroxyalkyl phenyl selenides and **1** represents the key intermediate in the present procedure.

Initially, we attempted to anchor the β-hydroxyalkyl phenyl selenides to **1** via an ether linkage directly under Mitsunobu reaction conditions [triphenylphosphine/diethyl azodicarboxylate (TPP/DEAD)] [15], but the conversion of the ionic liquid-supported hydroxyethyl group to ether bond was not complete. Interestingly however, after a considerable number of experiments, β-hydroxyalkyl phenyl selenides were almost quantitatively anchored to **1** via two-step reaction. In the first step, reaction of **1** with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (DBU) [16] afforded the trichloroacetimide intermediate **2**. The complete conversion of the hydroxy group of **1** to ionic-liquid-supported trichloroacetimide **2** was confirmed by treating **2** with acetyl chloride/triethylamine: no acetoxy absorption band was observed in the IR spectrum of the product. β-Hydroxyalkyl phenyl selenides were then loaded onto the trichloroacetimide derivative of ionic liquid **2** through the action of $BF_3{\cdot}OEt_2$ to give ionic liquid-supported α-phenylselenomethyl ether **3**, which was confirmed by the complete disappearance of the strong C═N stretching band near 1662 cm^{-1}. After this, the resulting ether **3** was subjected to the deselenation reaction directly with 30% hydrogen peroxide at 0°C and then at room temperature to afford the corresponding ionic liquid-supported vinyl ether **4**, which was found to have lost all its selenium by elemental analysis of **4**, indicating the oxidation–elimination was complete.

Then, 1,3-dipolar cycloaddition of **4** with nitrile oxides was investigated. Herein, the ionic liquid-supported vinyl ether **4** was reacted with nitrile oxides generated *in situ* from commercially available ethyl chlorooximidoacetate in the presence of triethylamine to form ionic liquid-supported ethyl isoxazoline-3-carboxylate **5**. The formation of the ionic liquid-supported isoxazoline **5** was also easily monitored by IR spectroscopy for the appearance of a new carbonyl stretching near 1720 cm^{-1}. The subsequent cleavage of **5** to give products **6** was achieved by treatment of **5** with trifluoroacetic acid in dichloromethane. On completion of the reaction, the crude product was purified by flash chromatography on silica gel to afford ethyl 5-substituted isoxazole-3-carboxylate **6**, which was characterized by conventional techniques (^1H and ^{13}C NMR and IR). As shown in Table 1, this method was found to be generally applicable, and all the products as a single regioisomer were obtained in good overall yields (78–90%).

Finally, the typical Suzuki reaction of the ionic liquid-supported intermediate **5f** with phenylboronic acid under similar reaction conditions [17] was further investigated (Scheme 2). Treatment of **5f** with phenylboronic acid in the presence of a catalytic amount of $Pd(OAc)_2$ in an aqueous solution of cesium fluoride under nitrogen at 80°C for 20 h gave the crude product, which was purified by evaporation of the reaction mixture under reduced pressure, followed by extraction of the crude product with ether to afford the Suzuki coupling intermediate **7**. Cleavage of **7** with the same protocol as aforementioned produced the target compound **8** in 82%.

It is worthy of note that, in each step of the sequence, the ionic liquid-supported intermediates were purified by washing with diethyl ether. The excess reaction reagents

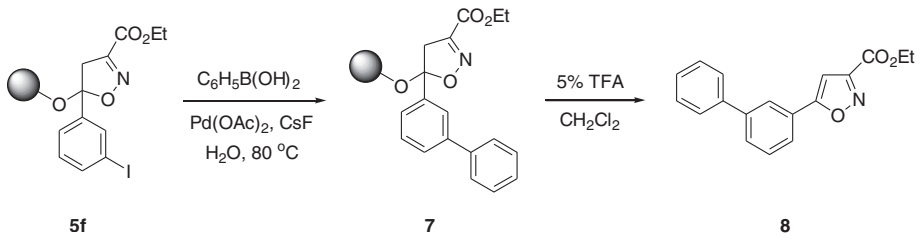
Table 1

The yields of ethyl isoxazole-3-carboxylates (**6a–6k**).

Entry	R	Product	Yield (%)[a]
1	C_6H_5	**6a**	82
2	4-$CH_3C_6H_4$	**6b**	90
3	4-$CH_3OC_6H_4$	**6c**	90
4	3-$CH_3OC_6H_4$	**6d**	88
5	4-ClC_6H_4	**6e**	86
6	3-IC_6H_4	**6f**	85
7	4-FC_6H_4	**6g**	84
8	$C_6H_5OCH_2$	**6h**	81
9	$C_6H_5CH_2OCH_2$	**6i**	80
10	$CH_3(CH_2)_3OCH_2$	**6j**	78
11	CH_3	**6k**	78

[a]Overall yields based on [2-hydemim][BF4] (**1**).

Scheme 2. Suzuki reaction of **5f** with phenylboronic acid.



5f **7** **8**

and the by-products were removed by simple decantation. Moreover, the ionic liquid [2-hydemim][BF_4] (**1**) could be typically recovered (the yield of recovered **1** was ≥90%) and reused with no appreciable decrease in yields and reaction activity.

CONCLUSIONS

In summary, we report an efficient and new method for the synthesis of ethyl isoxazoline-3-carboxylates by 1,3-dipolar cycloaddition of ionic liquid-supported vinyl ethers, derived from ionic liquid-supported α-phenylselenomethyl ether, with ethyl cyanoformate *N*-oxide, and subsequent cleavage from ionic liquid support under acidic conditions. Compared with previously reported methods, this new method using the ionic liquid as soluble support offers many advantages such as environmental friendliness, much higher loading capacity, easy isolation and purification of the products, recyclability of the soluble support, and so on. Additionally, a typical example of Suzuki coupling reaction was applied to prepare 5-biphenyl-substituted-isoxazoline-3-carboxylate for extending this methodology. Further investigations based on the ionic liquid-supported vinyl ether reagents are now in progress.

EXPERIMENTAL

FTIR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer (Waltham, MA). ^{1}H NMR (400 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer (Billerica, MA), using $CDCl_3$ or acetone-d_6 as both solvent and reference. Mass spectra (EI, 70 eV) were recorded on an HP5989B mass spectrometer (Palo Alto, CA). Microanalyses were performed with a Carlo Erba 1106 elemental analyzer (Milan, Italy). Melting points were measured on a Kofler melting point apparatus and are uncorrected. TLCs were performed on pre-coated plates of silica gel HF254 (0.5 mm, Qindao, China). Flash column chromatography was performed on silica gel H (Qindao, China). 1-(2-Hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([2-hydemim][BF_4], **1**) was prepared according to the literature method [18]. β-Hydroxyalkyl phenyl selenides were prepared by the reaction of benzeneselenolate ions with the corresponding epoxides according to the procedure reported previously [19]. The other chemicals were commercially available. All organic solvents were dried by standard methods.

Preparation of ionic-liquid-supported trichloroacetimide (2). To a solution of [2-hydemim][BF_4] (**1**) (2.8 g, 13 mmol) in dry CH_2Cl_2 (50 mL) was added trichloroaceonitrile (2.16 g, 15 mmol). After the mixture was cooled to 0°C, DBU (1.0 mL, 6.5 mmol) was added slowly, and the reaction was allowed to proceed at 0°C for 40 min, the solvent was eliminated in a rotary evaporator under reduced pressure. The resulting crude mixture was washed three times with anhydrous ether (15 × 3 mL) with vigorous magnetic stirring. After decantation, the residual solvent was removed *in vacuo*. The ionic liquid-supported trichloroacetimide (**2**) was further dried under high vacuum and led to a pale yellow viscous oil in 98% yield. IR (film): ν 1662 cm^{-1}.

General procedure for the preparation of ionic liquid-supported α-phenylselenomethyl ether (3). To a solution of **2** (5 mmol) and β-hydroxyalkyl phenyl selenide (7 mmol) in dry CH_2Cl_2 (25 mL) was added a catalytic amount of $BF_3{\cdot}OEt_2$. The mixture was stirred at room temperature for 30 min and then was concentrated under reduced pressure, and the resulting crude mixture was washed with anhydrous ether (15 × 3 mL) and dried under vacuum to give **3**.

3a. Yellow viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.89 (s, 1H), 7.69 (t, J = 1.6 Hz, 1H), 7.60 (t, J = 1.6 Hz, 1H), 7.45–7.42 (m, 2H), 7.34–7.20 (m, 8H), 4.52 (dd, J = 8.4, 5.2 Hz, 1H), 4.05 (s, 3H), 3.88 (t, J = 4.8 Hz, 2H), 3.70 (t, J = 4.8 Hz, 2H), 3.36 (dd, J = 12.4, 8.4 Hz, 1H), 3.11 (dd, J = 12.4, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 141.1, 137.1, 132.4, 130.8, 128.9, 128.5, 128.0, 126.8, 123.6, 122.8, 119.5, 80.5, 65.0, 52.1, 37.5, 35.5; IR (film): ν 3029, 2925, 1502, 1460, 1070 cm^{-1}.

3b. Yellow viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.89 (s, 1H), 7.69 (t, J = 1.6 Hz, 1H), 7.60 (t, J = 1.6 Hz, 1H), 7.55–7.53 (m, 2H), 7.24–7.20 (m, 3H), 7.16 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 4.49 (dd, J = 8.3, 5.3 Hz, 1H), 4.05 (s, 3H), 3.87 (t, J = 4.8 Hz, 2H), 3.69 (t, J = 4.8 Hz, 2H), 3.34 (dd, J = 12.2, 8.3 Hz, 1H), 3.09 (dd, J = 12.2, 5.3 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 140.2, 138.2, 137.0, 129.1, 128.7, 128.6, 127.5, 127.2, 126.9, 123.3, 122.7, 80.2, 65.4, 52.4, 37.3, 35.4, 20.5; IR (film): ν 3030, 2927, 1500, 1461, 1375, 1068 cm^{-1}.

3c. Yellow viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.91 (s, 1H), 7.70 (t, J = 1.6 Hz, 1H), 7.61 (t, J = 1.6 Hz, 1H), 7.34–7.22 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.50 (dd, J = 8.4, 5.6 Hz, 1H), 4.02 (s, 3H), 3.86 (t, J = 5.0 Hz, 2H), 3.80 (s, 3H), 3.68 (t, J = 5.0 Hz, 2H), 3.36 (dd, J = 12.4, 8.4 Hz, 1H), 3.15 (dd, J = 12.4, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 159.2, 137.5, 137.0, 135.4, 129.6, 129.2, 128.8, 127.3, 123.5, 122.8, 117.1, 79.8, 65.6, 54.8, 52.7, 36.8, 35.6; IR (film): ν 3028, 2925, 1505, 1464, 1378, 1065 cm^{-1}.

3d. Yellow viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.90 (s, 1H), 7.69 (t, J = 1.6 Hz, 1H), 7.60 (t, J = 1.6 Hz, 1H),

7.42–7.37 (m, 3H), 7.32–7.18 (m, 5H), 7.06 (s, 1H), 4.50 (dd, J = 8.3, 5.8 Hz, 1H), 4.03 (s, 3H), 3.90 (t, J = 4.8 Hz, 2H), 3.82 (s, 3H), 3.70 (t, J = 4.8 Hz, 2H), 3.36 (dd, J = 12.2, 8.3 Hz, 1H), 3.15 (dd, J = 12.2, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 155.6, 137.1, 135.5, 130.8, 129.4, 128.7, 127.8, 127.1, 123.5, 122.8, 120.8, 117.5, 112.2, 80.1, 65.5, 55.2, 52.5, 36.7, 35.4; IR (film): ν 3027, 2926, 1503, 1465, 1375, 1062 cm^{-1}.

3e. Pale yellow solid, mp 68–70°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.93 (s, 1H), 7.71–7.65 (m, 3H), 7.65 (t, J = 1.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.35–7.21 (m, 5H), 4.50 (dd, J = 8.2, 5.9 Hz, 1H), 4.06 (s, 3H), 3.90 (t, J = 5.0 Hz, 2H), 3.72 (t, J = 5.0 Hz, 2H), 3.28 (dd, J = 12.5, 8.2 Hz, 1H), 3.17 (dd, J = 12.5, 5.9 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 139.5, 136.5, 134.8, 129.8, 129.1, 128.8, 128.4, 128.0, 127.2, 123.6, 122.7, 79.8, 65.3, 52.4, 36.6, 35.7; IR (KBr): ν 3033, 2928, 1509, 1468, 1071 cm^{-1}.

3f. Pale yellow solid, mp 85–87°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.92 (s, 1H), 7.67 (t, J = 1.6 Hz, 1H), 7.59 (t, J = 1.6 Hz, 1H), 7.48–6.40 (m, 2H), 7.37–7.23 (m, 5H), 7.05–6.95 (m, 2H), 4.50 (dd, J = 8.3, 5.8 Hz, 1H), 4.05 (s, 3H), 3.89 (t, J = 4.8 Hz, 2H), 3.70 (t, J = 4.8 Hz, 2H), 3.32 (dd, J = 12.7, 8.3 Hz, 1H), 3.15 (dd, J = 12.7, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 139.5, 137.0, 136.5, 132.2, 131.0, 129.3, 128.9, 127.4, 127.3, 126.2, 123.8, 122.9, 97.1, 80.1, 65.6, 52.5, 36.8, 35.5; IR (KBr): ν 3031, 2926, 1505, 1466, 1068 cm^{-1}.

3g. Pale yellow solid, mp 57–59°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.90 (s, 1H), 7.67 (t, J = 1.6 Hz, 1H), 7.60 (t, J = 1.6 Hz, 1H), 7.50–7.45 (m, 2H), 7.35–7.15 (m, 7H), 4.47 (dd, J = 8.4, 5.8 Hz, 1H), 4.03 (s, 3H), 3.92 (t, J = 4.8 Hz, 2H), 3.70 (t, J = 4.8 Hz, 2H), 3.32 (dd, J = 12.6, 8.4 Hz, 1H), 3.15 (dd, J = 12.6, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 163.6 (d, $^1J_{c\text{-}F}$ = 250.0 Hz), 139.8, 136.7, 129.5, 129.3, 128.9, 127.1, 124.2, 123.5, 122.5, 116.8 (d, $^3J_{c\text{-}F}$ = 4.2 Hz), 80.3, 65.6, 52.4, 36.7, 35.3; IR (KBr): ν 3032, 2923, 1505, 1465, 1175, 1135, 1062 cm^{-1}.

3h. Yellow viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.86 (s, 1H), 7.67 (t, J = 1.6 Hz, 1H), 7.61 (t, J = 1.6 Hz, 1H), 7.52–7.50 (m, 2H), 7.30–7.20 (m, 5H), 7.01–7.92 (m, 3H), 4.15–4.09 (m, 3H), 4.05 (s, 3H), 3.92 (t, J = 5.0 Hz, 2H), 3.70 (t, J = 5.0 Hz, 2H), 3.24 (dd, J = 12.8, 6.4 Hz, 1H), 3.18 (dd, J = 12.8, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 150.5, 137.1, 132.6, 129.4, 129.1, 128.8, 127.0, 123.6, 122.8, 121.0, 117.5, 76.8, 69.1, 65.0, 52.1, 36.5, 30.2; IR (film): ν 3027, 2922, 1500, 1460, 1065 cm^{-1}.

3i. Yellow viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.88 (s, 1H), 7.68 (t, J = 1.6 Hz, 1H), 7.60 (t, J = 1.6 Hz, 1H), 7.50–7.47 (m, 2H), 7.37–7.20 (m, 8H), 4.50 (s, 2H), 4.06 (dt, J = 5.8, 1.6 Hz, 2H), 4.05 (s, 3H), 3.92 (t, J = 5.0 Hz, 2H), 3.74–3.70 (m, 3H), 3.15 (dd, J = 12.5, 6.0 Hz, 1H), 3.10 (dd, J = 12.6, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 138.5, 137.1, 132.6, 130.4, 129.0, 128.3, 127.6, 127.5, 126.8, 123.5, 122.7, 77.5, 73.3, 71.1, 65.2, 52.3, 36.5, 29.5; IR (film): ν 3028, 2923, 1501, 1458, 1066 cm^{-1}.

3j. Yellow viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.89 (s, 1H), 7.67 (t, J = 1.6 Hz, 1H), 7.62 (t, J = 1.6 Hz, 1H), 7.52–7.50 (m, 2H), 7.30–7.25 (m, 3H), 4.10 (dt, J = 6.0, 1.8 Hz, 2H), 4.02 (s, 3H), 3.93 (t, J = 5.0 Hz, 2H), 3.73–3.69 (m, 3H), 3.27 (t, J = 7.0 Hz, 2H), 3.27 (dd, J = 12.3, 6.0 Hz, 1H), 3.09 (dd, J = 12.3, 5.8 Hz, 1H), 1.55–1.50 (m, 2H), 1.38–1.32 (m, 2H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 137.0, 135.2, 129.2, 128.7, 127.2, 123.3, 122.5, 80.4, 73.4, 70.1, 65.2, 52.3, 36.3, 34.1, 32.9, 20.5, 15.1; IR (film): ν 3035, 2928, 1378, 1060 cm^{-1}.

3k. Yellow viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.88 (s, 1H), 7.66 (t, J = 1.6 Hz, 1H), 7.62 (t, J = 1.6 Hz, 1H), 7.52–7.50 (m, 2H), 7.30–7.25 (m, 3H), 4.02 (s, 3H), 3.95 (t, J = 5.0 Hz, 2H), 3.73–3.65 (m, 3H), 3.22 (dd, J = 12.3, 6.0 Hz, 1H), 3.09 (dd, J = 12.3, 5.8 Hz, 1H), 1.06 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 137.3, 135.7, 129.3, 128.8, 127.3, 123.4, 122.4, 77.4, 65.3, 52.3, 36.4, 34.5, 21.5; IR (film): ν 3035, 2930, 1498, 1380, 1058 cm^{-1}.

General procedure for the preparation of ionic liquid-supported vinyl ethers (4a–4k). To a solution of **3** (5 mmol) in CH_2Cl_2 (20 mL) was added 30% (aq) H_2O_2 (1.5 mL, 14.5 mmol), and the mixture was stirred for 30 min at 0°C, followed by 1 h at room temperature. After completion of the reaction, the solvent was evaporated and the crude mixture was washed with anhydrous ether (15 × 3 mL) and dried under vacuum to give **4**.

4a. Colorless viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 9.00 (s, 1H), 7.78 (t, J = 1.7 Hz, 1H), 7.65 (t, J = 1.7 Hz, 1H), 7.16–7.12 (m, 3H), 6.98–6.95 (m, 2H), 4.68 (d, J = 3.0 Hz, 1H), 4.25 (d, J = 3.0 Hz, 1H), 4.04 (s, 3H), 3.95 (t, J = 4.6 Hz, 2H), 3.77 (t, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 153.4, 137.2, 131.5, 129.8, 128.1, 127.3, 123.6, 122.8, 86.5, 62.9, 49.2, 35.5; IR (film): ν 3031, 2876, 1610, 1240, 994, 912 cm^{-1}.

4b. Colorless viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 9.01 (s, 1H), 7.79 (t, J = 1.7 Hz, 1H), 7.67 (t, J = 1.7 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.70 (d, J = 3.6 Hz, 1H), 4.36 (d, J = 3.6 Hz, 1H), 4.03 (s, 3H), 3.94 (t, J = 4.6 Hz, 2H), 3.72 (t, J = 4.6 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 153.7, 140.5, 137.0, 129.0, 128.8, 127.1, 123.5, 122.4, 86.8, 62.6, 49.1, 35.4, 21.5; IR (film): ν 3032, 2878, 1612, 1378, 1240, 990, 824 cm^{-1}.

4c. Colorless viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 9.89 (s, 1H), 7.77 (t, J = 1.7 Hz, 1H), 7.67 (t, J = 1.7 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 4.73 (d, J = 3.8 Hz, 1H), 4.35 (d, J = 3.8 Hz, 1H), 4.02 (s, 3H), 3.95 (t, J = 4.6 Hz, 2H), 3.83 (s, 3H), 3.72 (t, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 154.2, 153.3, 136.8, 127.8, 123.6, 122.6, 118.8, 116.5, 86.8, 62.3, 54.5, 49.0, 35.7; IR (film): ν 3036, 2978, 1610, 1375, 1242, 994, 834 cm^{-1}.

4d. Colorless viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 9.88 (s, 1H), 7.76 (t, J = 1.7 Hz, 1H), 7.67 (t, J = 1.7 Hz, 1H), 7.45–7.38 (m, 3H), 7.10 (s, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.36 (d, J = 3.8 Hz, 1H), 4.02 (s, 3H), 3.94 (t, J = 4.6 Hz, 2H), 3.84 (s, 3H), 3.73 (t, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 155.6, 153.5, 136.8, 130.2, 127.7, 123.6, 122.6, 120.1, 116.7, 112.8, 86.7, 62.3, 55.0, 49.1, 35.6; IR (film): ν 3032, 2982, 1612, 1377, 1240, 965 cm^{-1}.

4e. White solid, mp 137–139°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 9.91 (s, 1H), 7.78 (t, J = 1.7 Hz, 1H), 7.68 (t, J = 1.7 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 4.75 (d, J = 3.6 Hz, 1H), 4.41 (d, J = 3.6 Hz, 1H), 4.04 (s, 3H), 3.92 (t, J = 4.6 Hz, 2H), 3.75 (t, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 153.5, 137.0, 136.2, 129.5, 128.3, 126.8, 123.5, 122.6, 86.9, 62.5, 49.2, 35.6; IR (KBr): ν 3036, 2980, 1608, 1445, 1240, 996, 845 cm^{-1}.

4f. White solid, mp 152–154°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 9.90 (s, 1H), 8.10 (s, 1H), 7.78–776 (m, 2H), 7.70 (t, J = 1.7 Hz, 1H), 7.37–7.28 (m, 2H), 4.80 (d, J = 3.4 Hz, 1H), 4.42 (d, J = 3.4 Hz, 1H), 4.04 (s, 3H), 3.93 (t, J = 4.6 Hz, 2H), 3.75 (t, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 154.2, 139.0, 137.0, 134.3, 130.2, 129.0, 127.2, 125.6, 123.7, 122.7, 87.2, 62.6, 50.3, 35.7; IR (KBr): ν 3045, 2980, 1611, 1446, 1243, 990 cm^{-1}.

4g. White solid, mp 126–128°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 9.90 (s, 1H), 7.77 (t, J = 1.7 Hz, 1H), 7.67 (t, J = 1.7 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 4.78 (d, J = 3.6 Hz, 1H), 4.45 (d, J = 3.6 Hz, 1H), 4.03 (s, 3H), 3.91 (t, J = 4.6 Hz, 2H), 3.74 (t, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 164.0 (d, $^1J_{c\text{-}F}$ = 250.4 Hz), 153.8, 137.1, 129.5, 125.8, 123.5, 122.6, 117.8 (d, $^3J_{c\text{-}F}$ = 4.2 Hz), 86.9, 62.7, 49.9, 35.6; IR (KBr): v 3036, 2980, 1608, 1445, 1240, 1135, 996, 845 cm^{-1}.

4h. White solid, mp 67–69°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 9.87 (s, 1H), 7.72 (t, J = 1.7 Hz, 1H), 7.64 (t, J = 1.7 Hz, 1H), 7.50–7.47(m, 2H), 7.26–7.18 (m, 3H), 4.95 (d, J = 3.8 Hz, 1H), 4.56 (d, J = 3.8 Hz, 1H), 4.42 (s, 2H), 4.03 (s, 3H), 3.95 (t, J = 4.6 Hz, 2H), 3.72 (t, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 154.0, 137.0, 130.8, 123.6, 123.3, 122.6, 121.6, 115.0, 86.3, 65.6, 62.4, 49.1, 35.4; IR (film): v 3132, 2928, 1618, 1378, 1242, 965 cm^{-1}.

4i. White solid, mp 70–72°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 9.86 (s, 1H), 7.70 (t, J = 1.7 Hz, 1H), 7.62 (t, J = 1.7 Hz, 1H), 7.51–7.47 (m, 2H), 7.30–7.20 (m, 3H), 4.92 (d, J = 3.8 Hz, 1H), 4.53 (d, J = 3.8 Hz, 1H), 4.40 (s, 2H), 4.07 (s, 2H), 4.03 (s, 3H), 3.95 (t, J = 4.6 Hz, 2H), 3.72 (t, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 154.2, 137.1, 130.5, 129.0, 128.2, 125.8, 123.5, 122.6, 86.3, 73.4, 66.6, 62.4, 49.0, 35.5; IR (film): v 3135, 2930, 1620, 1375, 1240, 967 cm^{-1}.

4j. White solid, mp 46–48°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.87 (s, 1H), 7.69 (t, J = 1.6 Hz, 1H), 7.62 (t, J = 1.6 Hz, 1H), 4.92 (d, J = 3.8 Hz, 1H), 4.53 (d, J = 3.8 Hz, 1H), 4.12 (s, 2H), 4.02 (s, 3H), 3.95 (t, J = 4.6 Hz, 2H), 3.72 (t, J = 4.6 Hz, 2H), 3.32 (t, J = 7.0 Hz, 2H), 1.53–1.50 (m, 2H), 1.36–1.32 (m, 2H), 0.94 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 154.8, 137.0, 123.4, 122.5, 86.4, 74.4, 73.1, 62.2, 49.3, 35.3, 32.7, 19.8, 14.8; IR (film): v 3131, 2928, 1378, 1058 cm^{-1}.

4k. Colorless viscous oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.89 (s, 1H), 7.67 (t, J = 1.6 Hz, 1H), 7.64 (t, J = 1.6 Hz, 1H), 4.62 (d, J = 3.2 Hz, 1H), 4.43 (d, J = 3.2 Hz, 1H), 4.03 (s, 3H), 3.95 (t, J = 4.8 Hz, 2H), 3.72 (t, J = 4.8 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 152.8, 137.0, 123.5, 122.6, 85.4, 62.4, 49.1, 35.3, 22.5; IR (film): v 3045, 2830, 1365, 1050 cm^{-1}.

Ionic liquid-supported isoxazolines 5—General procedure for the preparation of ionic-liquid-supported vinyl ethers (5a–5k). To a stirred solution of **4** (5 mmol) in dry CH_2Cl_2 (20 mL) was first added Et_3N (2.1 mL, 15 mmol). Then ethyl chlorooximidoacetate (2.2 g, 14.5 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and added via syringe over 1 h, and the mixture was finally stirred overnight under nitrogen atmosphere at room temperature. After completion of the reaction, the solvent was evaporated, and the crude mixture was washed with anhydrous ether (15 × 3 mL) and dried under vacuum to give **5**.

5a. Pale yellow solid, mp 132–134°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.92 (s, 1H), 7.90 (t, J = 1.7 Hz, 1H), 7.01 (t, J = 1.7 Hz, 1H), 7.50–7.43 (m, 2H), 7.30–7.21 (m, 3H), 4.51 (t, J = 5.0 Hz, 2H), 4.02 (s, 3H), 3.97 (t, J = 5.0 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.50 (s, 2H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.3, 156.6, 136.8, 130.7, 128.9, 128.5, 126.8, 123.2, 122.6, 102.5, 65.0, 63.5, 52.1, 44.8, 35.6, 14.0; IR (KBr): v 3230, 2987, 1742, 1448, 1215 cm^{-1}.

5b. Pale yellow solid, mp 137–139°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.90 (s, 1H), 7.87 (t, J = 1.7 Hz, 1H), 7.68 (t, J = 1.7 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 4.50 (t, J = 5.0 Hz, 2H), 4.03 (s, 3H), 3.96 (t, J = 5.0 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.51 (s, 2H), 2.34 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.2, 156.3, 141.0, 136.9, 130.1, 127.5, 126.2, 123.3, 122.7, 102.8, 65.2, 63.4, 52.3, 44.4, 35.5, 20.2, 13.8; IR (KBr): v 3178, 2986, 1742, 1365, 1209, 910, 862 cm^{-1}.

5c. Pale yellow solid, mp 122–124°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.91 (s, 1H), 7.86 (t, J = 1.7 Hz, 1H), 7.70 (t, J = 1.7 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 4.48 (t, J = 5.0 Hz, 2H), 4.03 (s, 3H), 3.94 (t, J = 5.0 Hz, 2H), 3.81 (s, 3H), 4.36 (q, J = 7.2 Hz, 2H), 3.50 (s, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.1, 159.4, 156.0, 136.8, 128.7, 123.5, 122.5, 121.5, 115.4, 103.0, 65.3, 63.5, 55.4, 52.2, 44.1, 35.6, 13.9; IR (KBr): v 3201, 2981, 1746, 1605, 1362, 1209, 911, 846 cm^{-1}.

5d. Pale yellow solid, mp 101–103°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.90 (s, 1H), 7.87 (t, J = 1.7 Hz, 1H), 7.69 (t, J = 1.7 Hz, 1H), 7.42–7.26 (m, 3H), 6.98 (s, 1H), 4.48 (t, J = 5.0 Hz, 2H), 4.03 (s, 3H), 3.95 (t, J = 5.0 Hz, 2H), 3.83 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 3.54 (s, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.2, 159.0, 156.2, 137.0, 130.0, 129.7, 123.5, 122.5, 120.2, 117.4, 111.2, 103.2, 65.4, 63.5, 55.3, 52.4, 43.9, 35.5, 14.1; IR (KBr): v 3430, 2980, 1740, 1608, 1364, 1296, 1219, 1078, 913, 756 cm^{-1}.

5e. Pale yellow solid, mp 135–137°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.92 (s, 1H), 7.89 (t, J = 1.7 Hz, 1H), 7.71 (t, J = 1.7 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 4.51 (t, J = 5.0 Hz, 2H), 4.05 (s, 3H), 3.96 (t, J = 5.0 Hz, 2H), 4.40 (q, J = 7.0 Hz, 2H), 3.62 (s, 2H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 167.8, 155.7, 137.0, 135.5, 128.9, 128.6, 127.8, 123.6, 122.7, 103.8, 65.5, 62.1, 52.4, 44.5, 35.6, 14.1; IR (KBr): v 3190, 2985, 1748, 1365, 1230, 1139, 917, 865 cm^{-1}.

5f. Pale yellow solid, mp 156–158°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.91 (s, 1H), 7.88 (t, J = 1.7 Hz, 1H), 7.70 (t, J = 1.7 Hz, 1H), 7.48–6.40 (m, 3H), 7.03 (s, 1H), 4.50 (t, J = 5.0 Hz, 2H), 4.03 (s, 3H), 3.95 (t, J = 5.0 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 3.60 (s, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 166.5, 155.4, 137.1, 139.0, 134.3, 130.2, 129.0, 127.2, 125.6, 123.5, 122.6, 104.1, 65.4, 62.6, 52.2, 43.9, 35.6, 14.1; IR (KBr): v 3187, 2981, 1749, 1362, 1290, 1203, 923, 861 cm^{-1}.

5g. Pale yellow solid, mp 127–129°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.90 (s, 1H), 7.87 (t, J = 1.7 Hz, 1H), 7.69 (t, J = 1.7 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.52 (t, J = 4.8 Hz, 2H), 4.04 (s, 3H), 3.95 (t, J = 4.8 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.65 (s, 2H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.0, 163.9 (d, $^1J_{c\text{-}F}$ = 249.5 Hz), 162.5, 155.5, 137.1, 129.4, 123.6, 122.7, 116.6 (d, $^3J_{c\text{-}F}$ = 4.3 Hz), 103.6, 65.5, 63.8, 52.4, 44.3, 35.5, 14.4; IR (KBr): v 3192, 1747, 1361, 1292, 1208, 1135, 918, 866 cm^{-1}.

5h. Pale yellow solid, mp 60–62°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.90 (s, 1H), 7.86 (t, J = 1.7 Hz, 1H), 7.68 (t, J = 1.7 Hz, 1H), 7.51–7.46 (m, 2H), 7.27–7.20 (m, 3H), 4.50 (t, J = 5.0 Hz, 2H), 4.04 (s, 3H), 3.95 (t, J = 5.0 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.52 (s, 2H), 3.40 (s, 2H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 166.1, 155.2, 137.0, 131.2, 124.3, 123.5, 122.6, 121.2, 115.5, 102.7, 65.6, 63.5, 62.4, 52.4, 45.7, 35.6, 13.8; IR (KBr): v 3038, 2982, 1750, 1363, 1280, 1205, 963 cm^{-1}.

5i. Pale yellow solid, mp 65–67°C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.89 (s, 1H), 7.87 (t, J = 1.7 Hz, 1H), 7.68 (t, J = 1.7 Hz, 1H), 7.50–7.45 (m, 2H), 7.28–7.20 (m, 3H), 4.50 (t, J = 5.0 Hz, 2H), 4.03 (s, 3H), 3.95 (t, J = 5.0 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.56 (s, 2H), 3.44 (s, 2H), 3.37 (s, 2H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 165.3, 155.4, 137.0, 130.6, 129.3, 128.0, 126.8, 123.5, 122.6, 102.8, 65.5, 64.5, 63.1, 62.4, 52.6,

45.4, 35.5, 13.9; IR (KBr): *v* 3036, 2984, 1747, 1365, 1278, 1206, 965 cm^{-1}.

5j. Pale yellow viscous oil; ^1H NMR (400 MHz, acetone-d_6): δ 8.86 (s, 1H), 7.86 (t, *J* = 1.7 Hz, 1H), 7.66 (t, *J* = 1.7 Hz, 1H), 4.49 (t, *J* = 5.0 Hz, 2H), 4.02 (s, 3H), 3.96 (t, *J* = 5.0 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.56 (s, 2H), 4.36 (s, 2H), 3.35 (t, *J* = 7.0 Hz, 2H), 1.55–1.53 (m, 2H), 1.38–1.34 (m, 5H), 0.95 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 165.0, 155.1, 137.0, 123.6, 122.4, 103.2, 74.0, 67.8, 65.6, 62.4, 52.5, 44.6, 35.6, 32.5, 20.2, 15.0, 13.8; IR (film): *v* 3045, 2980, 1744, 1375, 1106 cm^{-1}.

5k. Colorless viscous oil; ^1H NMR (400 MHz, acetone-d_6): δ 8.88 (s, 1H), 7.88 (t, *J* = 1.7 Hz, 1H), 7.67 (t, *J* = 1.7 Hz, 1H), 4.50 (t, *J* = 5.0 Hz, 2H), 4.03 (s, 3H), 3.97 (t, *J* = 5.0 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.61 (s, 2H), 2.22 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 164.8, 155.3, 137.0, 123.5, 122.6, 103.0, 65.6, 62.2, 52.5, 44.6, 35.6, 22.6, 13.8; IR (film): *v* 3035, 2828, 1380, 1052 cm^{-1}.

General procedure for the preparation of ethyl isoxazole-3-carboxylates (6a–6k). To a solution of **5** (5 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (5%) and following stirring for 30 min. After removing the solvent under reduced pressure, the residue was extracted with ether (15 × 3 mL). The combined ether extracts were concentrated and the crude solution was purified by flash chromatography (silica gel, *n*-hexane-EtOAc, 10 : 1 to 3 : 1) to give the products **6a–6k**.

Ethyl 5-phenylisoxazole-3-carboxylate (6a).Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80–7.78 (m, 2H), 7.44–7.41 (m, 3H), 6.91 (s, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 160.2, 156.8, 130.9, 129.8, 128.2, 127.3, 100.7, 62.6, 14.5; MS (EI): *m/z* 217 (M^+); *Anal*. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.26; H, 5.17; N, 6.39; IR (film): *v* 3328, 2982, 1726, 1448, 1245, 1024 cm^{-1}.

Ethyl 5-(4-methylphenyl)isoxazole-3-carboxylate (6b).Pale yellow solid; mp 107–109°C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.90 (s, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 160.0, 156.9, 140.7, 129.3, 128.8, 127.2, 100.7, 62.7, 21.6, 14.5; MS (EI): *m/z* 231 (M^+); *Anal*. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.44; H, 5.76; N, 6.01; IR (KBr): *v* 3430, 2985, 1728, 1447, 1290, 1248, 1020, 820 cm^{-1}.

Ethyl 5-(4-methoxyphenyl)isoxazole-3-carboxylate (6c).Yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.88 (s, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 160.5, 157.1, 154.5, 127.3, 118.6, 113.8, 100.5, 62.5, 54.4, 14.0; MS (EI): *m/z* 247 (M^+); *Anal*. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.07; H, 5.38; N, 5.60; IR (film): *v* 3438, 2980, 1730, 1455, 1283, 1250, 1030, 830, 765 cm^{-1}.

Ethyl 5-(3-methoxyphenyl)isoxazole-3-carboxylate (6d).Yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.42 (m, 2H), 7.37–7.34 (m, 1H), 7.07–7.04 (m, 1H), 6.89 (s, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 161.7, 158.4, 156.6, 130.2, 127.6, 119.4, 116.6, 111.9, 100.2, 62.2, 55.3, 14.4; MS (EI): *m/z* 247 (M^+); *Anal*. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.06; H, 5.39; N, 5.61; IR (film): *v* 3445, 2978, 1735, 1452, 1251, 1032, 762 cm^{-1}.

Ethyl 5-(4-chlorophenyl)isoxazole-3-carboxylate (6e).Colorless solid; mp 124–125°C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.91 (s, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 160.7, 157.3, 136.5, 129.3, 128.1, 126.2, 100.3, 62.4, 14.2; MS (EI): *m/z* 251 (M^+); *Anal*. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01; N, 5.57. Found: C, 57.16; H, 4.10; N, 5.51; IR (KBr): *v* 3132, 2983, 1728, 1606, 1448, 1250, 1024, 828, 762 cm^{-1}.

Ethyl 5-(3-iodophenyl)isoxazole-3-carboxylate (6f).Colorless solid, mp 131–133°C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.28–7.24 (m, 2H), 6.95 (s, 1H), 4.48 (q, *J* = 7.0 Hz, 2H), 1.45 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 159.8, 156.8, 139.5, 134.3, 130.6, 129.3, 125.1, 127.2, 100.5, 62.3, 14.2; MS (EI): *m/z* 343 (M^+); *Anal*. Calcd for $C_{12}H_{10}INO_3$: C, 42.01; H, 2.94; N, 4.08. Found: C, 41.94; H, 3.03; N, 4.02; IR (KBr): *v* 3120, 2980, 1725, 1445, 1278, 1250 cm^{-1}.

Ethyl 5-(4-fluorophenyl)isoxazole-3-carboxylate (6g).Brownish solid, mp 108–110°C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85–7.81 (m, 2H), 7.26–7.22 (m, 2H), 6.91 (s, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 163.8 (d, $^1J_{c\text{-}F}$ = 250.6 Hz), 159.6, 156.5, 129.5, 124.3, 117.0 (d, $^3J_{c\text{-}F}$ = 4.2 Hz), 100.7, 62.4, 14.3; MS (EI): *m/z* 235 (M^+); *Anal*. Calcd for $C_{12}H_{10}FNO_3$: C, 61.28; H, 4.28; N, 5.96. Found: C, 61.20; H, 4.36; N, 5.91; IR (KBr): *v* 3133, 2986, 1728, 1445, 1245, 1022, 828 cm^{-1}.

Ethyl 5-phenoxymethylisoxazole-3-carboxylate (6h).Yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.29 (m, 2H), 6.90–6.79 (m, 3H), 6.87 (s, 1H), 4.52 (s, 2H), 4.45 (q, *J* = 7.0 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 160.2, 156.4, 130.6, 123.3, 121.8, 114.8, 101.2, 68.3, 62.1, 13.8; MS (EI): *m/z* 247 (M^+); *Anal*. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.05; H, 5.38; N, 5.60; IR (film): *v* 3130, 2928, 1731, 1590, 1455, 1250, 1060 cm^{-1}.

Ethyl 5-benzyloxymethylisoxazole-3-carboxylate (6i).Yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50–7.42 (m, 2H), 7.37–7.27 (m, 3H), 6.88 (s, 1H), 4.56 (s, 2H), 4.45 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 2H), 1.45 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 160.0, 156.2, 128.0, 127.5, 127.2, 122.1 101.8, 70.0, 62.4, 57.8, 14.3; MS (EI): *m/z* 261 (M^+); *Anal*. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.28; H, 5.85; N, 5.30; IR (film): *v* 3132, 2925, 1730, 1589, 1456, 1248, 1061 cm^{-1}.

Ethyl 5-(n-buoxymethyl)isoxazole-3-carboxylate (6j).Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 6.85 (s, 1H), 4.50 (s, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.61 (t, *J* = 7.0 Hz, 2H), 1.76–1.70 (m, 2H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.38–1.32 (m, 2H), 0.95 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 159.5, 156.0, 100.4, 70.1, 62.4, 56.3, 31.6, 19.2, 14.4, 13.8; MS (EI): *m/z* 227 (M^+); *Anal*. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.06; H, 7.62; N, 6.11; IR (film): *v* 2928, 1735, 1250, 1055 cm^{-1}.

Ethyl 5-Methylisoxazole-3-carboxylate (6k).Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 2.70 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 159.2, 155.8, 100.6, 62.2, 24.6, 14.5; MS (EI): *m/z* 155 (M^+); *Anal*. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.09; H, 5.92; N, 9.00; IR (film): *v* 2927, 1733, 1246, 1048 cm^{-1}.

Procedure for the preparation of ethyl 5-(3-phenylphenyl) isoxazole-3-carboxylate (8). To a solution of ionic liquid-supported ethyl 5-(3-iodophenyl)isoxazoline-3-carboxylates **5f** (1.41 g, 3 mmol) in 10 mL of degassed water at 80°C under nitrogen was added phenylboronic acid (0.55 g, 4.5 mmol) and CsF (0.90 g, 6 mmol) in one portion. The resulting mixture was stirred at this temperature for 15 min before 10 mol.% of Pd

$(OAc)_2$ (0.03 mmol) was added. The reaction system was then stirred vigorously for 20 h at 80°C under nitrogen atmosphere. On completion of the reaction, the solvent was removed in a rotary evaporator under reduced pressure. The residue was washed with ether (15×3 mL) and small amount of water (1 mL). After decanting the liquid phase, the crude product **7** was dried on vacuum pump, examined by NMR, and subjected to the next step of cleavage reaction to afford the product **8** in 82% yield based on **1**, according to the experimental procedure used for **6**. Colorless solid, mp 143–144°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, $J = 8.2$ Hz, 2H), 7.80–7.78 (m, 4H), 7.58 (s, 1H), 7.46–7.40 (m, 2H), 6.90 (s, 1H), 4.44 (q, $J = 7.2$ Hz, 2H), 1.44 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 160.1, 156.5, 133.2, 130.6, 129.5, 129.1, 128.8, 128.4, 128.0, 127.1, 122.3, 117.4, 100.5, 62.3, 14.2; MS (EI): *m/z* 293 (M^+); *Anal*. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.60; H, 5.25; N, 4.71; IR (KBr): *v* 3330, 2985, 1730, 1450, 1248, 1022 cm^{-1}.

Acknowledgments. We gratefully acknowledge financial support from the National Natural Science Foundation of China (No. 21062007), NSF of Jiangxi Province (No. 2009GZH0016), and the Research Program of Jiangxi Province Department of Education (No. GJJ10385, GJJ11380).

REFERENCES AND NOTES

[1] Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. Synthesis 1987, 857.

[2] Mares, D.; Romagnoli, C.; Tosi, B.; Benvegn, R.; Bruni, A.; Vicentini, C. B. Fungal Genet Biol 2002, 36, 47.

[3] Sobenia, L. N.; Drichkov, V. N.; Mikhaleva, A. I.; Petrova, O. V.; Ushakov, I. A.; Trofimov, B. A. Tetrahedron 2005, 61, 4841.

[4] Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. J Med Chem 2000, 43, 775.

[5] (a) Shen, D. M.; Shu, M.; Chapman, K. T. Org Lett 2000, 2, 2789; (b) Marzinzik, A. L.; Felder, E. R. Tetrahedron Lett 1996, 37, 1003.

[6] (a) Yedidia, V.; Leznoff, C. C. Can J Chem 1980, 58, 1144. (b) Pei, Y. Z.; Moos, W. H. Tetrahedron Lett 1994, 35, 5825. (c) Kantorowski, E. J.; Kurth, M. J. J Org Chem 1997, 62, 6797; (d) Haino, T.; Tanaka, M.; Ideta, K.; Kubo, K.; Mori, A.; Fukazawa, Y. Tetrahedron Lett 2004, 45, 2277; (e) Gao, D.; Zhai, H. M.; Parvez, M.; Back, T. G. J Org Chem 2008, 73, 8057.

[7] (a) Barrett, A. G. M.; Procopiou, P. A.; Voigtmann, U. Org Lett 2001, 3, 3165; (b) Engler, T. A. In Studies in Natural Product Chemistry; Attaur-Rahman, Ed.; Elsevier Science BV: New York, 1995; Vol 16.

[8] (a) Shankar, B. B.; Yang, D. Y.; Girton, S.; Ganguly, A. K. Tetrahedron Lett 1998, 39, 2447; (b) Alonso, C.; Nantz, M. H.; Kurth, M. J. Tetrahedron Lett 2000, 41, 5617.

[9] (a) Huang, X.; Xu, W. M. Org Lett 2003, 5, 4649; (b) Xu, W. M.; Wang, Y. G.; Miao, M. Z.; Huang, X. Synthesis 2005, 2143; (c) Xu, W. M.; Huang, X.; Tang, E. J Comb Chem 2005, 7, 726; (d) Sheng, S. R.; Xin, Q.; Liu, X. L.; Sun, W. K.; Guo, R.; Huang, X. Synthesis 2006, 2293; (e) Huang, X.; Wang, Y. G. J Comb Chem 2007, 9, 121; (f) Wang, Y. G.; Xu, W. M.; Huang, X. Synthesis 2007, 28; (g) Cao, J.; Huang, X. J Comb Chem 2008, 10, 526.

[10] For a review, see: (a) Guillier, F.; Orain, D.; Bradley, M. Chem Rev 2000, 100, 2091; (b) Sammelson, R. E.; Kurth, M. J. Chem Rev 2001, 101, 137; (c) Blaney, P.; Grigg, R.; Sridharan, V. Chem Rev 2002, 102, 2607; (d) Nandy, J. P.; Prakesch, M.; Khadem, S.; Reddy, P. T.; Sharma, U.; Arya, P. Chem Rev 2009, 109, 1999.

[11] For a review, see: (a) Gravert, D. J.; Janda, K. D. Chem Rev 1997, 97, 489; (b) Sun, C. M. Comb Chem High Throughput Screen 1999, 2, 299; (c) Toy, P. H.; Janda, K. D. Acc Chem Res 2000, 33, 546; (d) Dickerson, T. J.; Reed, N. N.; Janda, K. D. Chem Rev 2002, 102, 3325.

[12] For a review, see: (a) Davis, J. H. J. Chem Lett 2004, 33, 1072. (b) Chauhan, S. M. S.; Jain, N.; Kumar, A.; Chauhan, S. Tetrahedron 2005, 61, 1015; (c) Scott, J. L.; Shahana, C.; Mohan, R. S. Tetrahedron 2007, 63, 2363; (d) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. Chem Rev 2008, 108, 2015. (e) Hallett, J. P.; Welton, T. Chem Rev 2011, 111, 3508.

[13] Sheng, S. R.; Liu, X. L.; Xu, Q.; Song, C.-S. Synthesis 2003, 2763.

[14] Paulmier, C., Ed. Selenium Reagents and Intermediates in Organic Synthesis; Pergamon Press: Oxford, 1986.

[15] Mitsunobu, O. Synthesis 1981, 1.

[16] Hanessian, S.; Xie, F. Tetrahedron Lett 1998, 39, 733.

[17] (a) Wright, S. W.; Hageman, D. L.; McClure, L. D. J Org Chem 1994, 59, 6095; (b) Miao, W.; Chan, T. H. Org Lett 2003, 5, 5003.

[18] Branco, L. C.; Rosa, J. N.; Moura Ramos, J. J.; Afonso, C. A. M. Chem Eur J 2002, 8, 3671.

[19] Engman, L.; Gupta, V. J Org Chem 1997, 62, 157.