JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

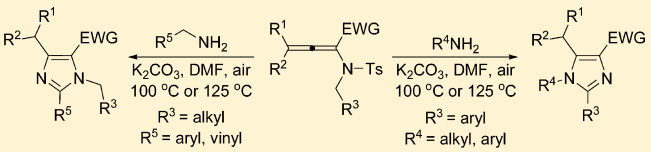
Regioselective Synthesis of Highly Substituted Imidazoles via the Sequential Reaction of Allenyl Sulfonamides and Amines

Lian Yu, Yuan Deng, and Jian Cao*

Key Laboratory of Organosilicon Chemistry and Material Technology of the Ministry of Education, Hangzhou Normal University, Wenyi Road 222, Hangzhou 310012, People's Republic of China

Supporting Information

ABSTRACT: A novel synthesis of imidazoles from electron-withdrawing group-substituted allenyl sulfonamides with amines was developed. The 4- and 5-functionalized imidazoles were constructed regioselectively, which depended on the substituents on the nitrogen atoms.



Imidazoles are an important class of heterocyclic compounds that are not only a fundamental motif found in various natural products but also a key structural unit in pharmaceutical compounds.[1] For example, Olmesartan **1**, an angiotensin II receptor antagonist,[2] consists of an imidazole-5-carboxylate unit (Figure 1). Imidazole-4-carboxamide compound **2** was discovered to be a potent and highly selective CB2 receptor antagonist,[3] and imidazolo-nectrisine-phosphono acid derivative **3** was found to be a potential glycosyltranferase inhibitor.[4] Recently, imidazoles have also been used as precursors to environmentally friendly ionic solvents[5] and carbene ligands.[6] Thus, the synthesis of functionalized imidazoles has attracted considerable attention, and many methods have been developed for their synthesis.[7] However, the reported methods for their synthesis can be limited with respect to the type and location of functional group substituents and regioselectivity. Therefore, it is still highly desirable to develop direct and efficient strategies that afford imidazoles derivatives.

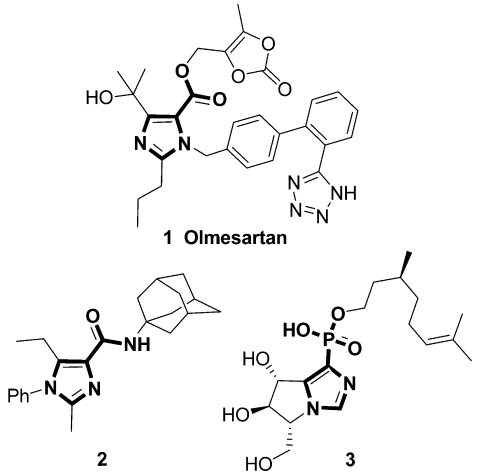


Figure 1. Several imidazole derivatives that have been reported as biologically active compounds and pharmaceutical products.

Allenamides and ynamides, special classes of functionalized allenes and alkynes, have recently received much attention in the synthetic community.[8,9] Various nitrogen-containing building blocks, including nitrogen heterocycles, were successfully synthesized from allenamides and ynamides.[10,11] Recently, Rabasso and co-workers reported a simple and efficient synthesis of α-amino allenephosphonates by the [2,3]-sigmatropic rearrangement of ynamido-alcohols[12] and selective reduction of amino allenephosphonates for the preparation of α-amino vinylphosphonates.[13] These α-amino allenephosphonates represent a kind of allene substituted with both electron-withdrawing and -donating groups; thus, they show some special reactivity. In the continuation of our investigation of allenamides[14] and ynamides,[15] we recently found a novel synthesis of imidazoles from electron-withdrawing group-substituted allenyl sulfonamides with amines. Herein, we report the regioselective synthesis of highly substituted imidazoles.

We initiated our studies by examining the reaction of allenyl sulfonamide **4a** with propylamine **5a**. Imidazole **6a** was not detected when **4a** and **5a** were reacted in CH_3CN at room temperature (Table 1, entry 1). Fortunately, in the presence of a base (K_2CO_3), the reaction in refluxing CH_3CN gave imidazole **6a** in 39% yield (entry 2). Addition of 2 equiv of **5a** gave a better yield (entry 3). Subsequent screening of solvent and base showed that DMF proved to be the most suitable solvent (entries 4–7), whereas K_2CO_3 was the best base (entries 8–10). Thus, we concluded that K_2CO_3 as base in DMF at 100 °C under air provided the sole product imidazole **6a** in the highest yield (87%, entry 5).

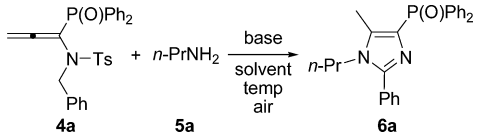
Under the optimized conditions, the scope of this reaction was further investigated. A variety of amines, including primary alkyl amines (n-$PrNH_2$, n-$BuNH_2$, i-$BuNH_2$, and $PhCH_2CH_2NH_2$), secondary alkyl amines (i-$PrNH_2$ and $C_6H_{11}NH_2$), and aryl amines (p-$MeOC_6H_4NH_2$ and $PhNH_2$), were all efficiently coupled to furnish the corresponding product imidazoles (Table 2, entries 1–8 and 11). Both α-

Received: January 20, 2015
Published: April 8, 2015

 © 2015 American Chemical Society

DOI: 10.1021/acs.joc.5b00141
J. Org. Chem. 2015, 80, 4729–4735

Table 1. Optimization of the Reaction Conditions[a]



4a 5a 6a

entry	base	solvent	temp (°C)	time (h)	yield of **6a** (%)
1	no	CH_3CN	rt	12	0
2	K_2CO_3	CH_3CN	reflux	8	39
3[b]	K_2CO_3	CH_3CN	reflux	8	54
4[b]	K_2CO_3	1,4-dioxane	100	2	66
5[b]	K_2CO_3	DMF	100	2	87
6[b]	K_2CO_3	toluene	100	2	41
7[b]	K_2CO_3	DMSO	100	2	75
8[b]	*i*-Pr_2EtN	DMF	100	2	50
9[b]	K_3PO_4	DMF	100	2	72
10[b]	Cs_2CO_3	DMF	100	2	80

[a]Unless otherwise specified, the reaction was carried out using **4a** (0.2 mmol), **5a** (0.2 mmol), and base (0.6 mmol) in solvent (2 mL) under air. [b]**5a** (0.4 mmol) was used.

amino allenephosphonates and allenephosphine oxides worked well to afford corresponding imidazol-4-ylphosphonates and imidazol-4-ylphosphine oxides, respectively. R^1 and R^2 groups on the allene moiety could be H, alkyl, and aryl, although bulky groups resulted in lower yields (entries 9–13). The R^3 group of **4** could be a substituted by a phenyl group (entries 1 and 12). α-Amino allenoates could also undergo this reaction under modified conditions (entries 14–17). In all reactions in Table 2, the 4-functionalized imidazole was obtained as the sole regioisomer, and the structure was revealed by X-ray diffraction of **6c**.[16]

The reaction of allenyl sulfonamide **4g** with $BnNH_2$ **5i** under standard conditions afforded the expected imidazole-4-carboxylate **6q**. Interestingly, a regioisomer, imidazole-5-carboxylate **7a**, was also found (Scheme 1).[17] The corresponding regioisomer was not detected in the ^1H NMR spectra of the crude reaction mixtures when other alkyl amines were employed (Table 2).

Realizing that the substituents on the nitrogen atoms could play an important role in the regioselectivity, we conducted reactions of various amines with allenyl sulfonamides in which R^3 was an alkyl group. As shown in Table 3, *N*-propyl allenyl sulfonamides **4i** and **4j** reacted with substituted benzyl amines **5i**–**5k** to produce imidazole-5-carboxylates **7b**–**7d** and imidazol-5-ylphosphine oxide **7g**. 2-Picolylamine **5l** and allylamine **5m** also gave the imidazoles products, albeit in lower yields (entries 4 and 5). The structure of **7g** was revealed by X-ray diffraction.[18] In these cases, regioisomers of the 4-functionalized imidazoles were not detected in the ^1H NMR spectra of the crude reaction mixtures. Thus, this reaction could regioselectively construct two regioisomers (e.g., **6a** and **7g**; **6m** and **7b**) just by exchanging the substituents on the two nitrogen atoms. However, the reaction of allenyl sulfonamide **4i** with an alkyl amine, such as *n*-$PrNH_2$ **5a**, resulted in an unidentified mixture (entry 7), indicating that at least one Bn or allyl group on the nitrogen atoms was necessary for this transformation.

To gain more insight into the reaction mechanism, we attempted to isolate the intermediate addition product of allenyl sulfonamides **4g** and **4i** with amines **5i** and **5c** (Scheme 2). Without a base, the reaction at room temperature gave the addition products **8a**–**8c**[19] (the structure was revealed by X-ray diffraction of **8a**[20]) in high yield, and no imidazole was found. Under the standard conditions, **8a**–**8c** were converted to imidazoles **6** and/or **7**. The regioselectivity was consistent with the results of the one-pot reactions, indicating that **8** was the intermediate of this sequential reaction.

On the basis of the above experimental observations, the following plausible mechanism was proposed for this reaction, as shown in Scheme 3. Initially, the addition reaction of allenyl sulfonamide **4** with amine **5** affords intermediate **A**. In the presence of K_2CO_3, elimination of one molecule of 4-methylbenzenesulfinic acid[21] provides an unstable diimine, **B**. Depending on the nature of substitutents at R^3 and R^5, **B** could be further converted to either **C** or **D** via a 1,5-H shift followed by concomitant ring closure.[22] Imidazoles **6** or **7** are thus forged through oxidative aromatization under open air conditions. Substituents R^3 and R^5 have extremely important roles in the product distribution. (i) When either R^3 or R^5 is an aryl or vinyl group, a benzylic or allylic proton may facilitate a 1,5-H shift, leading to intermediate **C** or **D**, respectively. (ii) Paths a and b coexist if both R^3 and R^5 are aryl groups, generating two sets of imidazoles. However, due to the electron-withdrawing effect of the attached ester group, the proton adjacent to R^3 shows stronger acidity, resulting in the predominance of intermediate **C**. (iii) In the case that neither R^3 nor R^5 is an aryl group, a 1,5-H shift process may be inhibited without an activated proton; therefore, no imidazole is produced.

In conclusion, we have described a novel regioselective synthesis of highly substituted imidazoles from electron-withdrawing group-substituted allenyl sulfonamides with amines. The imidazol-4- or imidazol-5-ylphosphonates, phosphine oxides, and carboxylates were constructed regioselectively, which depended on the substituents on the nitrogen atoms.

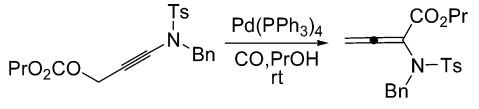
EXPERIMENTAL SECTION

General. All commercially available chemicals and reagents were used without any further purification. NMR spectra were recorded on a 400 or 500 MHz NMR spectrometer using tetramethylsilane as the internal standard and $CDCl_3$ as solvent. Chemical shifts are expressed in ppm, and *J* values are given in Hz. High-resolution mass spectrometry (HRMS) was obtained using the ESI^- or EI- or APCI-TOF method. Melting points were measured on a microscopic apparatus and were uncorrected.

Preparation of the α-amino allenephosphonates and phosphine oxides was done according to Rabasso's method.[12] Characterization of unreported α-amino allene phosphine oxide is listed below.

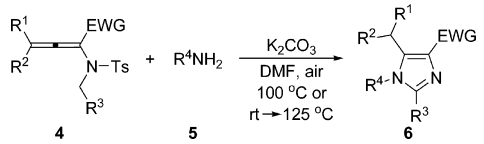
***N*-(1-(Diphenylphosphoryl)propa-1,2-dienyl)-4-methyl-*N*-propylbenzenesulfonamide (4j).** Colorless solid (556.6 mg, 56%). mp 146–148 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81–7.85 (m, 4H), 7.59–7.61 (m, 2H), 7.44–7.51 (m, 6H), 7.17–7.19 (m, 2H), 5.07 (s, 1H), 5.05 (s, 1H), 3.33 (t, *J* = 8.0 Hz, 2H), 2.34 (s, 3H), 1.45–1.55 (m, 2H), 0.73 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.0 (d, *J* = 22.0 Hz), 143.6, 135.7, 132.1, 131.9, 130.8, 129.3, 128.3, 128.0, 103.9 (d, *J* = 124.0 Hz), 84.0 (d, *J* = 9.6 Hz), 52.2, 21.5, 21.2, 11.0; IR (KBr): ν (cm^{-1}) 3060, 2980, 1384, 1197, 1157, 555, 524; HRMS (EI-TOF) *m*/*z*: M^+ calcd for $C_{25}H_{26}NO_3PS$, 451.1371; found, 451.1363.

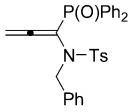
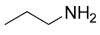
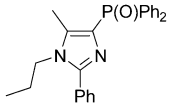
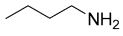
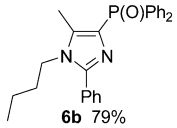
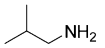
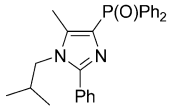
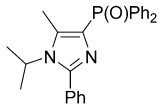
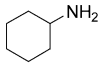
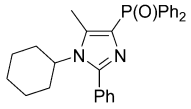
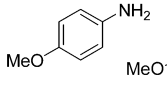
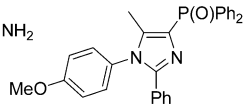
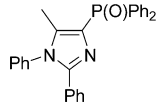
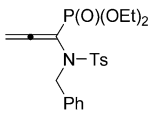
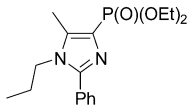
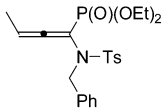
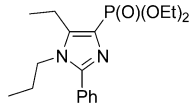
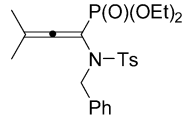
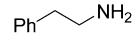
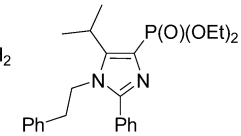
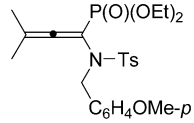
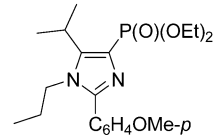
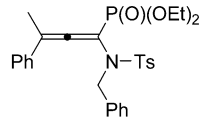
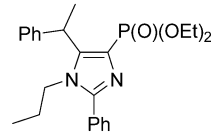
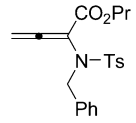
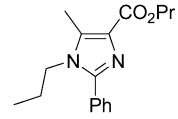
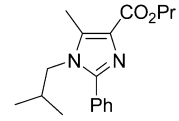
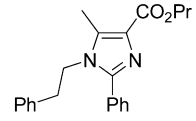
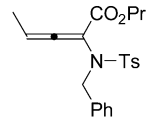
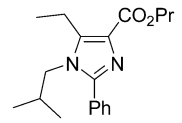
Propyl 2-(*N*-Benzyl-4-methylphenylsulfonamido)buta-2,3-dienoate (4g). Typical Procedure.



DOI: 10.1021/acs.joc.5b00141
J. Org. Chem. 2015, 80, 4729–4735

Table 2. Synthesis of 4-Functionalized Imidazoles 6[a]



entry	4	5	yield of 6
1	 **4a**	 **5a**	 **6a** 87%
2[b]	**4a**	**5a**	**6a** 77%
3	**4a**	 **5b**	 **6b** 79%
4	**4a**	 **5c**	 **6c** 86%
5	**4a**	 **5d**	 **6d** 30%
6	**4a**	 **5e**	 **6e** 53%
7	**4a**	 **5f**	 **6f** 47%
8	**4a**	PhNH2 **5g**	 **6g** 40%
9	 **4b**	**5a**	 **6h** 62%
10	 **4c**	**5a**	 **6i** 58%
11	 **4d**	 **5h**	 **6j** 28%
12	 **4e**	**5a**	 **6k** 48%
13	 **4f**	**5a**	 **6l** 45%
14[c]	 **4g**	**5a**	 **6m** 60%
15[c]	**4g**	**5c**	 **6n** 65%
16[c]	**4g**	**5h**	 **6o** 57%
17[c]	 **4h**	**5c**	 **6p** 73%

[a]Unless otherwise specified, the reaction was carried out using **4** (1.0 equiv), **5** (2.0 equiv), and K_2CO_3 (3.0 equiv) in DMF at 100 °C under air for 2−9 h. [b]Yield of a gram-scale reaction (**4a** 5.0 mmol, 2.498 g). [c]The reaction was carried out under air at rt for 1 h and then at 125 °C for 4−9 h.

To a flame-dried Schlenk flask were added 3-(*N*-benzyl-4-methylphenylsulfonamido)prop-2-ynyl propyl carbonate[14] (200.8 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol). After addition of each chemical, the flask was degassed and refilled with CO by a balloon of CO (about 1 L) three times. Then, PrOH (1 mL) was added, and the resulting mixture was stirred at rt for 24 h. After that, the resulting mixture was filtered through a short pad of silica gel, eluted with EtOAc (20 mL), and concentrated. The residue was purified by column chromatography on silica gel with hexane/EtOAc (9:1, v/v) as the eluent to obtain **4g** (48.0 mg, 25%) as a yellow oil. ^1H

DOI: 10.1021/acs.joc.5b00141
J. Org. Chem. 2015, 80, 4729−4735

Scheme 1. Synthesis of Imidazoles 6q and 7a

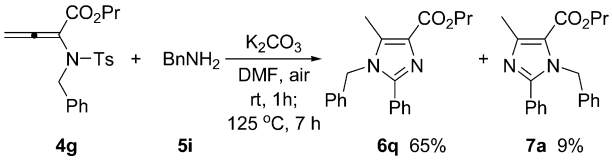
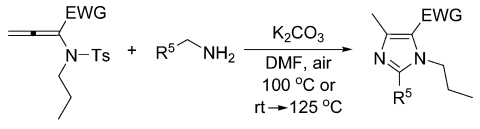


Table 3. Synthesis of 5-Functionalized Imidazoles 7[a]



entry	4	EWG	5	R^5	yield of 7 (%)
1	**4i**	CO_2Pr	**5i**	Ph	**7b**, 57
2	**4i**	CO_2Pr	**5j**	4-ClC_6H_4	**7c**, 53
3	**4i**	CO_2Pr	**5k**	3-$MeOC_6H_4$	**7d**, 47
4	**4i**	CO_2Pr	**5l**	2-pyridinyl	**7e**, 37
5	**4i**	CO_2Pr	**5m**	vinyl	**7f**, 20
6[b]	**4j**	$P(O)Ph_2$	**5i**	Ph	**7g**, 36
7	**4i**	CO_2Pr	**5a**	Et	unidentified mixture

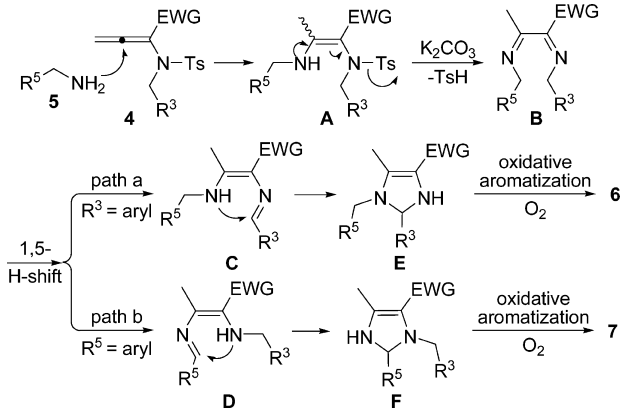
[a]Unless otherwise specified, the reaction was carried out using **4** (1.0 equiv), **5** (2.0 equiv), and K_2CO_3 (3.0 equiv) in DMF under air at rt for 1 h and then at 125 °C for 6–9 h. [b]The reaction was carried out at 100 °C for 3 h.

NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.24–7.26 (m, 5H), 5.21 (s, 2H), 4.44 (s, 2H), 4.03 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.57–1.62 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.8, 163.9, 143.8, 135.5, 135.4, 129.5, 128.6, 128.4, 128.0, 127.8, 104.6, 84.5, 67.1, 53.2, 21.9, 21.6, 10.3; IR (neat): ν (cm^{-1}) 2968, 1719, 1349, 1268, 1161, 1090, 666; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}NO_4S$, 386.1421; found, 386.1420.

Propyl 2-(*N*-Benzyl-4-methylphenylsulfonamido)penta-2,3-dienoate (4h). Yellow oil (61.9 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.0 Hz, 2H), 7.22–7.33 (m, 7H), 5.59 (q, J = 7.6 Hz, 1H), 4.44 (s, 2H), 4.02 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 1.58–1.62 (m, 2H), 1.50 (d, J = 7.6 Hz, 3H), 0.89 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.1, 164.3, 143.7, 135.7, 135.6, 129.5, 128.5, 128.3, 128.0, 127.7, 103.3, 96.0, 66.9, 52.9, 21.9, 21.6, 12.9, 10.3; IR (neat): ν (cm^{-1}) 2967, 1718, 1349, 1270, 1161, 1091, 665; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}NO_4S$, 400.1577; found, 400.1573.

Propyl 2-(4-Methyl-*N*-propylphenylsulfonamido)buta-2,3-dienoate (4i). Yellow oil (37.7 mg, 22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.35 (s, 2H), 4.11 (t, J = 6.8 Hz, 2H), 3.21 (t, J = 7.2 Hz, 2H), 2.42 (s, 3H), 1.49–1.68 (m, 4H), 0.87–0.96 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.4, 164.2, 143.5, 135.5, 129.3, 127.9, 104.7, 84.4, 67.2, 51.2, 21.9, 21.5, 21.4; IR (neat): ν (cm^{-1}) 2967, 1722, 1347, 1267, 1154, 1088, 1010; HRMS (APCI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{24}NO_4S$, 338.1421; found, 338.1434.

Scheme 3. Possible Mechanism

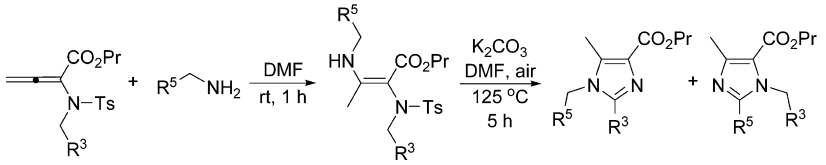


4-(Diphenylphosphoryl)-5-methyl-2-phenyl-1-propyl-1*H*-imidazole (6a). Typical Procedure. To a solution of α-amino allenephosphine oxides **4a** (99.9 mg, 0.2 mmol) in DMF (2 mL) were added amine **5a** (23.6 mg, 0.4 mmol) and K_2CO_3 (82.8 mg, 0.6 mmol), and the solution was stirred at 100 °C under air. Upon reaction completion (2 h, TLC, eluent: hexane/EtOAc 1:1), the mixture was filtered over a plug of silica gel (washed with 50 mL of EtOAc), and the filtrate was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with hexane/EtOAc (1:1–1:2, v/v) as the eluent to obtain **6a** (69.7 mg, 87%) as a colorless solid. mp 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.98 (m, 4H), 7.51–7.52 (m, 2H), 7.35–7.46 (m, 9H), 3.84 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 1.61–1.63 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0 (d, J = 18.5 Hz), 139.7 (d, J = 27.2 Hz), 134.6 (d, J = 106.5 Hz), 131.7 (d, J = 9.7 Hz), 131.3, 131.0, 129.11, 129.07, 128.6, 128.1 (d, J = 12.1 Hz), 126.7, 46.0, 23.9, 11.1, 10.2; IR (KBr): ν (cm^{-1}) 2969, 1438, 1176, 699, 568, 529; HRMS (EI-TOF) m/z: M^+ calcd for $C_{25}H_{25}N_2OP$, 400.1705; found, 400.1709.

1-Butyl-4-(diphenylphosphoryl)-5-methyl-2-phenyl-1*H*-imidazole (6b). Colorless solid (81.5 mg, 79%). mp 155–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93–7.98 (m, 4H), 7.51–7.53 (m, 2H), 7.38–7.45 (m, 9H), 3.89 (t, J = 8.0 Hz, 2H), 2.64 (s, 3H), 1.58–1.62 (m, 2H), 1.19–1.25 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (d, J = 18.6 Hz), 139.6 (d, J = 27.0 Hz), 134.9 (d, J = 106.5 Hz), 131.7 (d, J = 9.9 Hz), 131.2 (d, J = 2.7 Hz), 131.1, 129.1, 129.0, 128.6, 128.1 (d, J = 12.0 Hz), 127.7 (d, J = 157.9 Hz), 44.2, 32.5, 19.8, 13.5, 10.2; IR (KBr): ν (cm^{-1}) 2967, 1541, 1436, 1366, 1171, 1117, 697; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{28}N_2OP$, 415.1934; found, 415.1924.

4-(Diphenylphosphoryl)-1-isobutyl-5-methyl-2-phenyl-1*H*-imidazole (6c). Colorless solid (88.6 mg, 86%). mp 161–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.97 (m, 4H), 7.50–7.52 (m, 2H), 7.38–7.44 (m, 9H), 3.81 (d, J = 7.6 Hz, 2H), 2.63 (s, 3H), 1.77–1.81 (m, 1H), 0.68 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2 (d, J = 18.3 Hz), 139.9 (d, J = 26.9 Hz), 134.9 (d, J = 106.4 Hz), 131.7 (d, J = 9.7 Hz), 131.6, 131.2 (d, J = 2.5 Hz), 129.3, 128.9, 128.5,

Scheme 2. Isolation of the Intermediate 8



DOI: 10.1021/acs.joc.5b00141
J. Org. Chem. 2015, 80, 4729–4735

128.1 (d, J = 12.2 Hz), 127.7 (d, J = 148.3 Hz), 51.3, 29.1, 19.7, 10.6; IR (KBr): ν (cm^{-1}) 2970, 1542, 1436, 1261, 1181, 1117, 780, 698; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{28}N_2OP$, 415.1934; found, 415.1927.

4-(Diphenylphosphoryl)-1-isopropyl-5-methyl-2-phenyl-1*H*-imidazole (6d). Colorless solid (51.3 mg, 30%). mp 193−195 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.95−7.99 (m, 4H), 7.41−7.48 (m, 11H), 4.57−4.61 (m, 1H), 2.79 (s, 3H), 1.48 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.3 (d, J = 18.9 Hz), 139.1 (d, J = 27.5 Hz), 134.9 (d, J = 106.4 Hz), 131.8, 131.7, 131.2, 129.8, 129.1, 128.4, 128.5 (d, J = 147.2 Hz), 128.1 (d, J = 11.9 Hz), 48.9, 22.0, 11.8; IR (KBr): ν (cm^{-1}) 3049, 2967, 1368, 1166, 1135, 703, 535; HRMS (EI-TOF) m/z: M^+ calcd for $C_{25}H_{25}N_2OP$, 400.1705; found, 400.1697.

1-Cyclohexyl-4-(diphenylphosphoryl)-5-methyl-2-phenyl-1*H*-imidazole (6e). Yellow oil (70.0 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.82−7.88 (m, 4H), 7.28−7.33 (m, 11H), 4.00−4.02 (m, 1H), 2.68 (s, 3H), 1.71−1.84 (m, 6H), 1.53−1.56 (m, 1H), 1.03−1.12 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5 (d, J = 18.8 Hz), 139.2 (d, J = 27.1 Hz), 134.8 (d, J = 106.3 Hz), 131.8, 131.7, 131.2 (d, J = 2.7 Hz), 129.7, 129.1, 128.4, 128.3 (d, J = 151.0 Hz), 128.1 (d, J = 12.0 Hz), 57.8, 32.1, 26.1, 25.1, 12.1; IR (neat): ν (cm^{-1}) 3051, 2965, 1344, 1159, 1130, 704; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{30}N_2OP$, 441.2090; found, 441.2091.

4-(Diphenylphosphoryl)-1-(4-methoxyphenyl)-5-methyl-2-phenyl-1*H*-imidazole (6f). Yellow oil (65.9 mg, 47%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.02−8.07 (m, 4H), 7.43−7.46 (m, 6H), 7.34−7.36 (m, 2H), 7.18−7.20 (m, 3H), 7.08 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 148.3 (d, J = 17.7 Hz), 141.5 (d, J = 26.9 Hz), 134.7 (d, J = 106.5 Hz), 131.8, 131.7, 131.3 (d, J = 2.4 Hz), 130.3, 129.2, 129.0, 128.4, 128.2, 128.1 (d, J = 3.7 Hz), 128.0 (d, J = 147.9 Hz), 114.9, 55.5, 10.7; IR (neat): ν (cm^{-1}) 3029, 1513, 1437, 1250, 1170, 1120, 692; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{29}H_{26}N_2O_2P$, 465.1726; found, 465.1730.

4-(Diphenylphosphoryl)-5-methyl-1,2-diphenyl-1*H*-imidazole (6g). Yellow oil (51.9 mg, 40%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94−8.00 (m, 4H), 7.36−7.41 (m, 9H), 7.22−7.25 (m, 2H), 7.09−7.14 (m, 5H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1 (d, J = 17.8 Hz), 141.1 (d, J = 26.9 Hz), 136.7, 134.7 (d, J = 106.6 Hz), 131.8, 131.7, 131.3 (d, J = 2.6 Hz), 130.2, 129.8, 129.2, 128.4, 128.3, 128.2 (d, J = 147.4 Hz), 128.1, 128.0 (d, J = 13.1 Hz), 10.7; IR (neat): ν (cm^{-1}) 3027, 1510, 1435, 1244, 1169, 690; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{24}N_2OP$, 435.1621; found, 435.1614.

Diethyl 5-Methyl-2-phenyl-1-propyl-1*H*-imidazol-4-ylphosphonate (6h). Yellow oil (52.0 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.52−7.54 (m, 2H), 7.43−7.45 (m, 3H), 4.15−4.23 (m, 4H), 3.87 (t, J = 7.6 Hz, 2H), 2.58 (s, 3H), 1.61−1.67 (m, 2H), 1.35 (t, J = 7.5 Hz, 6H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1 (d, J = 22.1 Hz), 138.8 (d, J = 38.7 Hz), 130.8, 129.1, 129.0, 128.5, 125.2 (d, J = 243.8 Hz), 62.0 (d, J = 5.6 Hz), 46.1, 23.7, 16.2 (d, J = 6.5 Hz), 10.9, 10.1; IR (neat): ν (cm^{-1}) 3010, 1470, 1277, 1235, 1023, 957, 784; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{26}N_2O_3P$, 337.1676; found, 337.1657.

Diethyl 5-Ethyl-2-phenyl-1-propyl-1*H*-imidazol-4-ylphosphonate (6i). Yellow oil (201.5 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.54−7.56 (m, 2H), 7.41−7.45 (m, 3H), 4.14−4.25 (m, 4H), 3.90 (t, J = 8.0 Hz, 2H), 3.01 (q, J = 7.6 Hz, 2H), 1.57−1.63 (m, 2H), 1.26−1.36 (m, 9H), 0.80 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8 (d, J = 22.2 Hz), 144.6 (d, J = 39.0 Hz), 130.9, 129.0, 128.9, 128.4, 124.5 (d, J = 243.1 Hz), 61.8 (d, J = 5.6 Hz), 45.9, 24.1, 17.4, 16.2 (d, J = 6.4 Hz), 15.1, 10.8; IR (neat): ν (cm^{-1}) 2968, 1476, 1237, 1025, 948, 762; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{28}N_2O_3P$, 351.1832; found, 351.1839.

Diethyl 5-Isopropyl-1-phenethyl-2-phenyl-1*H*-imidazol-4-ylphosphonate (6j). Colorless solid (59.2 mg, 28%). mp 230−232 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.44−7.48 (m, 5H), 7,21−7.22 (m, 3H), 6.87 (d, J = 10.0 Hz, 2H), 4.15−4.24 (m, 6H), 3.55−3.58 (m, 1H), 2.78 (t, J = 8.0 Hz, 2H), 1.50 (d, J = 7.5 Hz, 6H), 1.36 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.6 (d, J = 22.4 Hz), 147.6 (d, J = 39.5 Hz), 136.9, 131.0, 129.4, 129.2, 128.2, 128.5, 128.4, 127.0, 124.6 (d, J = 242.5 Hz), 62.1 (d, J = 5.5 Hz), 46.4, 37.2, 25.3, 21.9, 16.4 (d, J = 6.5 Hz); IR (KBr): ν (cm^{-1}) 3031, 2927, 1263, 1227, 1055, 1027, 973; HRMS (EI-TOF) m/z: M^+ calcd for $C_{24}H_{31}N_2O_3P$, 426.2072; found, 426.2068.

Diethyl 5-Isopropyl-2-(4-methoxyphenyl)-1-propyl-1*H*-imidazol-4-ylphosphonate (6k). Yellow oil (144.3 mg, 48%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 4.13−4.22 (m, 4H), 3.85−3.89 (m, 5H), 3.42−3.46 (m, 1H), 1.58−1.63 (m, 2H), 1.50 (d, J = 9.5 Hz, 6H), 1.35 (t, J = 7.0 Hz, 6H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 148.3 (d, J = 22.1 Hz), 147.6 (d, J = 39.0 Hz), 130.7, 124.1 (d, J = 243.1 Hz), 123.6, 113.9, 62.0 (d, J = 5.5 Hz), 55.3, 46.5, 25.2, 24.4, 21.8, 16.3 (d, J = 6.5 Hz), 11.0; IR (neat): ν (cm^{-1}) 2926, 1456, 1266, 1050, 1022, 966; HRMS (EI-TOF) m/z: M^+ calcd for $C_{20}H_{31}N_2O_4P$, 394.2021; found, 394.2014.

Diethyl 2-Phenyl-5-(1-phenylethyl)-1-propyl-1*H*-imidazol-4-ylphosphonate (6l). Yellow oil (47.7 mg, 45%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 4.0 Hz, 2H), 7.28−7.39 (m, 7H), 7.19−7.22 (m, 1H), 5.42 (q, J = 7.5 Hz, 1H), 4.18−4.29 (4H, m), 3.63 (t, J = 8.5 Hz, 2H), 1.80 (d, J = 7.5 Hz, 3H), 1.34−1.40 (m, 6H), 1.03−1.07 (m, 1H), 0.62−0.66 (m, 1H), 0.37 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6 (d, J = 22.2 Hz), 145.3 (d, J = 38.9 Hz), 141.9, 131.0, 129.1, 128.9, 128.5, 127.3, 124.6, 125.7 (d, J = 242.3 Hz), 62.2, 46.8, 33.6, 23.0, 18.3, 16.4, 10.8; IR (neat): ν (cm^{-1}) 2973, 1226, 1023, 961, 779, 762, 699; HRMS (EI-TOF) m/z: M^+ calcd for $C_{24}H_{31}N_2O_3P$, 426.2072; found, 426.2068.

5-(Diphenylphosphoryl)-4-methyl-2-phenyl-1-propyl-1*H*-imidazole (7g). Colorless solid (36.0 mg, 36%). mp 152−154 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.68−7.73 (m, 4H), 7.42−7.57 (m, 11H), 4.24 (t, J = 7.0 Hz, 2H), 1.60 (s, 3H), 1.38−1.42 (m, 2H), 0.52 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.1 (d, J = 11.1 Hz), 147.6 (d, J = 15.2 Hz), 133.0 (d, J = 110.1 Hz), 132.3 (d, J = 2.6 Hz), 131.9 (d, J = 10.5 Hz), 130.5, 129.3, 129.1, 128.8 (d, J = 12.4 Hz), 128.6, 117.6 (d, J = 123.0 Hz), 48.1, 24.6, 15.4, 10.7; IR (KBr): ν (cm^{-1}) 2981, 2870, 1245, 724, 700, 559, 530; HRMS (EI-TOF) m/z: M^+ calcd for $C_{25}H_{25}N_2OP$, 400.1705; found, 400.1702.

Propyl 5-Methyl-2-phenyl-1-propyl-1*H*-imidazole-4-carboxylate (6m). Typical Procedure. To the solution of α-amino allene carboxylate **4g** (119.3 mg, 0.3 mmol) in DMF (2 mL) were added amine **5a** (35.5 mg, 0.6 mmol) and K_2CO_3 (124.4 mg, 0.9 mmol), and the solution was stirred at room temperature for 1 h and then at 125 °C under air. Upon reaction completion (7 h, TLC, eluent: hexane/EtOAc 1:1), the mixture was filtered over a plug of silica gel (washed with 50 mL of EtOAc), and the filtrate was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with hexane/EtOAc (1:1−1:2, v/v) as the eluent to obtain **6m** (51.6 mg, 60%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44−7.46 (m, 2H), 7.33−7.35 (m, 3H), 4.20 (t, J = 6.8 Hz, 2H), 3.79 (t, J = 7.6 Hz, 2H), 2.52 (s, 3H), 1.69−1.75 (m, 2H), 1.51−1.56 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H), 0.72 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 147.4, 136.3, 130.7, 129.3, 129.1, 128.8, 128.4, 65.8, 46.0, 23.7, 22.2, 10.9, 10.5, 10.4; IR (neat): ν (cm^{-1}) 2950, 1699, 1570, 1199, 1153, 1066, 711; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{23}N_2O_2$, 287.1754; found, 287.1745.

Propyl 1-Isobutyl-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (6n). Colorless solid (92.0 mg, 65%). mp 112−114 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52−7.54 (m, 2H), 7.41−7.42 (m, 3H), 4.29 (t, J = 7.2 Hz, 2H), 3.80 (d, J = 7.6 Hz, 2H), 2.60 (s, 3H), 1.78−1.84 (m, 3H), 0.99 (t, J = 7.2 Hz, 3H), 0.69 (d, J = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2, 147.7, 136.6, 131.1, 129.5, 129.0, 128.7, 128.4, 65.8, 51.4, 29.1, 22.2, 19.6, 10.8, 10.4; IR (KBr): ν (cm^{-1}) 2972, 1689, 1332, 1205, 1070, 785; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_2$, 301.1911; found, 301.1900.

Propyl 5-Methyl-1-phenethyl-2-phenyl-1*H*-imidazole-4-carboxylate (6o). Colorless solid (59.5 mg, 57%). mp 94−96 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.45 (m, 5H), 7.19−7.20 (m, 3H), 6.86−6.88 (m, 2H), 4.28 (t, J = 7.2 Hz, 2H), 4.13 (t, J = 7.6 Hz, 2H), 2.79 (t, J = 7.2 Hz, 2H), 2.49 (s, 3H), 1.78−1.83 (m, 2H), 0.99 (d, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 147.4, 136.8,

DOI: 10.1021/acs.joc.5b00141
J. Org. Chem. 2015, 80, 4729−4735

136.4, 130.6, 129.3, 129.2, 128.8, 128.7, 128.6, 128.4, 127.0, 65.8, 45.8, 36.6, 22.2, 10.5, 10.4; IR (KBr): ν (cm^{-1}) 2969, 1710, 1405, 1335, 1166, 1104, 1074; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{25}N_2O_2$, 349.1911; found, 349.1907.

Propyl 5-Ethyl-1-isobutyl-2-phenyl-1*H*-imidazole-4-carboxylate (6p). Colorless solid (115.0 mg, 73%). mp 71−73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.46 (m, 2H), 7.30−7.36 (m, 3H), 4.21 (t, J = 6.8 Hz, 2H), 3.73 (d, J = 7.2 Hz, 2H), 2.95 (q, J = 7.6 Hz, 2H), 1.71−1.74 (m, 3H), 1.18 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 0.60 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 147.6, 142.5, 131.2, 129.4, 129.0, 128.4, 128.1, 65.8, 51.4, 29.4, 22.2, 19.6, 18.0, 14.0, 10.4; IR (KBr): ν (cm^{-1}) 2971, 1692, 1336, 1199, 1090, 1009, 784; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_2$, 315.2067; found, 315.2060.

Propyl 1-Benzyl-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (6q). Colorless solid (138.1 mg, 65%). mp 96−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.52 (m, 2H), 7.28−7.36 (m, 6H), 6.96 (d, J = 7.2 Hz, 2H), 5.18 (s, 2H), 4.30 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 1.78−1.84 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 148.1, 136.9, 136.0, 130.0, 129.27, 129.24, 129.1, 128.5, 127.8, 125.5, 65.9, 48.0, 22.2, 10.5, 10.4; IR (KBr): ν (cm^{-1}) 2960, 1692, 1572, 1404, 1326, 1206, 1068; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_2$, 335.1754; found, 335.1750.

Propyl 1-Benzyl-4-methyl-2-phenyl-1*H*-imidazole-5-carboxylate (7a). Yellow oil (19.8 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.52 (m, 2H), 7.23−7.41 (m, 6H), 6.95 (d, J = 7.2 Hz, 2H), 5.58 (s, 2H), 4.14 (t, J = 6.4 Hz, 2H), 2.60 (s, 3H), 1.62−1.68 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 151.4, 148.2, 138.1, 129.8, 129.6, 129.2, 128.7, 128.6, 127.2, 125.6, 119.6, 65.9, 49.7, 22.0, 16.1, 10.6; IR (neat): ν (cm^{-1}) 2957, 1697, 1452, 1416, 1274, 1163, 1098; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_2$, 335.1754; found, 335.1757.

Propyl 4-Methyl-2-phenyl-1-propyl-1*H*-imidazole-5-carboxylate (7b). Yellow oil (83.0 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.55 (m, 2H), 7.46−7.48 (m, 3H), 4.23−4.28 (m, 4H), 2.55 (s, 3H), 1.68−1.83 (m, 4H), 1.05 (t, J = 7.6 Hz, 3H), 0.78 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 150.9, 148.0, 130.4, 129.4, 129.3, 128.6, 119.1, 65.9, 47.9, 24.7, 22.2, 16.1, 10.9, 10.7; IR (neat): ν (cm^{-1}) 2965, 1696, 1420, 1268, 1189, 1118, 1093; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{23}N_2O_2$, 287.1754; found, 287.1737.

Propyl 2-(4-Chlorophenyl)-4-methyl-1-propyl-1*H*-imidazole-5-carboxylate (7c). Colorless solid (68.4 mg, 53%). mp 57−59 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.51 (m, 4H), 4.21−4.28 (m, 4H), 2.54 (s, 3H), 1.67−1.83 (m, 4H), 1.05 (t, J = 7.6 Hz, 3H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 149.7, 148.0, 135.6, 130.6, 128.9, 119.4, 66.0, 47.9, 24.7, 22.1, 16.1, 10.9, 10.7; IR (KBr): ν (cm^{-1}) 2970, 1698, 1468, 1407, 1267, 1189, 1127, 842; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{22}ClN_2O_2$, 321.1364; found, 321.1355.

Propyl 2-(3-Methoxyphenyl)-4-methyl-1-propyl-1*H*-imidazole-5-carboxylate (7d). Yellow oil (60.0 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.31 (m, 1H), 7.01−7.03 (m, 2H), 6.92 (d, J = 8.4 Hz, 1H), 4.15−4.20 (m, 4H), 3.77 (s, 3H), 2.47 (s, 3H), 1.60−1.75 (m, 4H), 0.97 (t, J = 7.2 Hz, 3H), 0.71 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 159.2, 150.7, 147.9, 131.5, 129.6, 121.5, 119.1, 115.5, 114.6, 65.9, 55.4, 47.9, 24.8, 22.1, 16.2, 10.9, 10.7; IR (neat): ν (cm^{-1}) 2965, 1679, 1472, 1414, 1268, 1168, 1119; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_3$, 317.1860; found, 317.1855.

Propyl 4-Methyl-1-propyl-2-(pyridin-2-yl)-1*H*-imidazole-5-carboxylate (7e). Colorless solid (43.0 mg, 37%). mp 44−46 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.67−7.71 (m, 1H), 7.18−7.21 (m, 1H), 4.79 (t, J = 7.6 Hz, 2H), 4.19 (t, J = 6.4 Hz, 2H), 2.47 (s, 3H), 1.69−1.75 (m, 4H), 0.97 (t, J = 7.6 Hz, 3H), 0.78 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 150.2, 148.6, 147.5, 147.1, 136.6, 124.5, 123.2, 120.5, 65.9, 48.0, 24.6, 22.1, 16.3, 10.9, 10.7; IR (KBr): ν (cm^{-1}) 2964, 1697, 1586, 1410, 1267, 1203, 1124; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}N_3O_2$, 288.1707; found, 288.1700.

Propyl 4-Methyl-1-propyl-2-vinyl-1*H*-imidazole-5-carboxylate (7f). Yellow oil (18.7 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (dd, J_1 = 16.8 Hz, J_2 = 11.2 Hz, 1H), 6.28 (d, J = 16.8 Hz, 1H), 5.49 (t, J = 11.2 Hz, 1H), 4.14−4.21 (m, 4H), 2.43 (s, 3H), 1.65−1.71 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H), 0.85 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 148.0, 147.5, 122.1, 121.5, 118.7, 65.9, 46.3, 24.6, 22.1, 16.2, 11.0, 10.7; IR (neat): ν (cm^{-1}) 2966, 1696, 1405, 1270, 1156, 1119, 759; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{21}N_2O_2$, 237.1598; found, 237.1590.

(*E*)-Propyl 2-(*N*-Benzyl-4-methylphenylsulfonamido)-3-(benzylamino)but-2-enoate (8a). Typical Procedure. To the solution of α-amino allene carboxylate **4g** (242.9 mg, 0.63 mmol) in DMF (2 mL) was added amine **5g** (135.0 mg, 1.26 mmol), and the solution was stirred at room temperature. Upon reaction completion (1 h, TLC, eluent: hexane/EtOAc 1:1), the mixture was diluted with 50 mL of EtOAc and washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with hexane/EtOAc (1:1−1:2, v/v) as the eluent to obtain **8a** (268.4 mg, 86%) as a colorless solid. mp 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (br, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.23−7.32 (m, 10H), 7.06 (d, J = 7.2 Hz, 2H), 5.04 (d, J = 13.2 Hz, 1H), 4.29−4.32 (m, 2H), 4.09 (d, J = 13.2 Hz, 1H), 3.90−3.93 (m, 1H), 3.10−3.13 (m, 1H), 2.42 (s, 3H), 1.56 (s, 3H), 1.11−1.17 (m, 2H), 0.73 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 168.2, 142.5, 138.3, 137.8, 136.3, 130.4, 129.1, 128.8, 128.2, 127.70, 127.68, 127.4, 126.6, 93.7, 64.5, 53.6, 47.2, 21.6, 21.4, 15.6, 10.6; IR (KBr): ν (cm^{-1}) 2949, 1636, 1594, 1452, 1276, 1236, 1152, 1073; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_4S$, 493.2156; found, 493.2155.

(*E*)-Propyl 2-(*N*-Benzyl-4-methylphenylsulfonamido)-3-(isobutylamino)but-2-enoate (8b). Colorless solid (217.4 mg, 79%). mp 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (br, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.25−7.31 (m, 7H), 5.02 (d, J = 13.2 Hz, 1H), 4.06 (d, J = 13.2 Hz, 1H), 3.88−3.94 (m, 1H), 3.05−3.11 (m, 1H), 2.84−2.91 (m, 2H), 2.41 (s, 3H), 1.67−1.71 (m, 1H), 1.51 (s, 3H), 1.09−1.15 (m, 2H), 0.87 (t, J = 6.4 Hz, 6H), 0.73 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 168.2, 142.4, 138.3, 136.5, 130.4, 129.0, 128.1, 127.6, 92.7, 64.3, 53.7, 51.1, 29.0, 21.6, 21.4, 20.0, 15.6, 10.6; IR (KBr): ν (cm^{-1}) 2951, 1634, 1590, 1449, 1269, 1155; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{35}N_2O_4S$, 459.2312; found, 459.2311.

(*E*)-Propyl 3-(Benzylamino)-2-(4-methyl-*N*-propylphenylsulfonamido)but-2-enoate (8c). Colorless solid (261.4 mg, 84%). mp 60−62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (br, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.22−7.38 (m, 7H), 4.47−4.49 (m, 2H), 3.79−3.85 (m, 1H), 3.60−3.67 (m, 1H), 3.00−3.09 (m, 2H), 2.39 (s, 3H), 2.24 (s, 3H), 1.47−1.61 (m, 2H), 1.04−1.07 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H), 0.66 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 167.0, 142.3, 137.9, 137.7, 129.0, 128.9, 127.7, 127.6, 127.0, 95.0, 64.4, 52.3, 47.7, 22.0, 21.5, 21.4, 16.5, 11.4, 10.4; IR (KBr): ν (cm^{-1}) 2968, 1650, 1329, 1273, 1155, 662; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_2O_4S$, 445.2156; found, 445.2163.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds and crystal structure and data (in CIF format) for **6c**, **7g**, and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: caojian@hznu.edu.cn.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.joc.5b00141
J. Org. Chem. 2015, 80, 4729−4735

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (project no. 21102029) and Zhejiang Provincial Natural Science Foundation of China (project no. LY14B020013) for financial support.

■ REFERENCES

(1) (a) Grimmett, M. R. In *Science of Synthesis*; Neier, R., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2002; Vol. *12*, pp 325−528. (b) Iinuma, Y.; Kozawa, S.; Ishiyama, H.; Tsuda, M.; Fukushi, E.; Kawabata, J.; Fromont, J.; Kobayashi, J. *J. Nat. Prod.* **2005**, *68*, 1109. (c) Zhang, L.; Peng, X.; Damu, G. L. V.; Geng, R.; Zhou, C. *Med. Res. Rev.* **2014**, *34*, 340.

(2) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein J. Org. Chem.* **2011**, *7*, 442.

(3) Lange, J. H. M.; Van der Neut, M. A. W.; Wals, H. C.; Kuil, G. D.; Borst, A. J. M.; Mulder, A.; den Hartog, A. P.; Zilaout, H.; Goutier, W.; Van Stuivenberg, H. H.; Van Vliet, B. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1084.

(4) Tschamber, T.; Gessier, F.; Neuburger, M.; Gurcha, S. S.; Besra, G. S.; Streith, J. *Eur. J. Org. Chem.* **2003**, 2792.

(5) (a) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667. (b) Smith, T. W.; Zhao, M.; Yang, F.; Smith, D.; Cebe, P. *Macromolecules* **2013**, *46*, 1133.

(6) (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Gupta, S. K.; Ghorai, D.; Choudhury, J. *Organometallics* **2014**, *33*, 3215. (c) Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2013**, *135*, 14548.

(7) For examples, see: (a) Pusch, S.; Opatz, T. *Org. Lett.* **2014**, *16*, 5430. (b) Pooi, B.; Lee, J.; Choi, K.; Hirao, H.; Hong, S. H. *J. Org. Chem.* **2014**, *79*, 9231. (c) Yamauchi, T.; Shibahara, F.; Murai, T. *J. Org. Chem.* **2014**, *79*, 7185. (d) Chen, C.; Hu, W.; Yan, P.; Senadi, G. C.; Wang, J. *Org. Lett.* **2013**, *15*, 6116.

(8) For recent reviews on the chemistry of allenamides, see: (a) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (b) Lu, T.; Lu, Z.; Ma, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2013**, *113*, 4862.

(9) For recent reviews on the chemistry of ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (c) Evano, G.; Jouvin, K.; Coste, A. *Synthesis* **2013**, *45*, 17. (d) Wang, X.; Yeom, H.; Fang, L.; He, S.; Ma, Z.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560.

(10) For examples on allenamides, see: (a) Lohse, A. G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3430. (b) Persson, A. K. Å.; Bäckvall, J. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 4624. (c) Skucas, E.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 5054. (d) Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2011**, *13*, 3114. (e) Krenske, E. H.; He, S.; Huang, J.; Du, Y.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2013**, *135*, 5242.

(11) For examples on ynamides, see: (a) Fadel, A.; Legrand, F.; Evano, G.; Rabasso, N. *Adv. Synth. Catal.* **2011**, *353*, 263. (b) Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012**, *134*, 9078. (c) Gati, W.; Couty, F.; Boubaker, T.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Org. Lett.* **2013**, *15*, 3122. (d) Brioche, J.; Meyer, C.; Cossy, J. *Org. Lett.* **2013**, *15*, 1626. (e) Yao, P.-Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. *Org. Lett.* **2008**, *10*, 4275.

(12) Gomes, F.; Fadel, A.; Rabasso, N. *J. Org. Chem.* **2012**, *77*, 5439.

(13) Adler, P.; Gomes, F.; Fadel, A.; Rabasso, N. *Eur. J. Org. Chem.* **2013**, 7546.

(14) Cao, J.; Kong, Y.; Deng, Y.; Lai, G.; Cui, Y.; Hu, Z.; Wang, G. *Org. Biomol. Chem.* **2012**, *10*, 9556.

(15) (a) Kong, Y.; Jiang, K.; Cao, J.; Fu, L.; Yu, L.; Lai, G.; Cui, Y.; Hu, Z.; Wang, G. *Org. Lett.* **2013**, *15*, 422. (b) Kong, Y.; Yu, L.; Fu, L.; Cao, J.; Lai, G.; Cui, Y.; Hu, Z.; Wang, G. *Synthesis* **2013**, *45*, 1975. (c) Kong, Y.; Yu, L.; Cui, Y.; Cao, J. *Synthesis* **2014**, *46*, 183. (d) Yu, L.; Cao, J. *Org. Biomol. Chem.* **2014**, *12*, 3986. (e) Yu, L.; Deng, Y.; Cao, J. *Synthesis* **2015**, *47*, 783.

(16) CCDC 1043496.

(17) **7a** was transferred to corresponding ethyl ester with NaOEt/EtOH, and its ^{1}H NMR data was in accordance to reported data; see: Preti, L.; Attanasi, O. A.; Caselli, E.; Favi, G.; Ori, C.; Davoli, P.; Felluga, F.; Prati, F. *Eur. J. Org. Chem.* **2010**, 4312.

(18) CCDC 1043494.

(19) ^{1}H NMR spectra of the crude reaction mixtures showed mixtures of *Z*/*E* (about 1:2) stereoisomers. The *Z*-isomer was converted to *E*-isomer spontaneously during the course of flash chromatography on silica gel.

(20) CCDC 1043495.

(21) Similar elimination reaction of 4-methylbenzenesulfinic acid was observed in ours previous work; see: Cao, J.; Xu, Y.; Kong, Y.; Cui, Y.; Hu, Z.; Wang, G.; Deng, Y.; Lai, G. *Org. Lett.* **2012**, *14*, 38.

(22) (a) Cao, J.; Yang, X.; Hua, X.; Deng, Y.; Lai, G. *Org. Lett.* **2011**, *13*, 478. (b) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226. (c) Barluenga, J.; Fananas-Mastral, M.; Aznar, F.; Valdes, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6594. (d) Mori, K.; Kawasaki, T.; Sueoka, S.; Akiyama, T. *Org. Lett.* **2010**, *12*, 1732.

DOI: 10.1021/acs.joc.5b00141
J. Org. Chem. 2015, 80, 4729−4735