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Catalytic C−H Allylation and Benzylation of Pyrazoles

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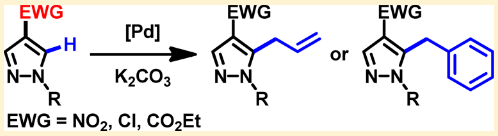
Supporting Information



ABSTRACT: We describe a general approach for the synthesis of allylated and benzylated pyrazoles. An electron-withdrawing substituent, such as nitro, chloro, and ester groups, at C4 renders the Lewis basic nitrogen atom to be less basic and the C−H bond more acidic than the ones of the parent ring, enabling Pd-catalyzed C−H allylation and benzylation reactions of pyrazoles. The new method expanding the scope of the C−H functionalization of pyrazoles beyond arylation reactions provides a rapid access to complex pyrazole compounds.

Pyrazoles have been found in a growing number of new pharmaceuticals, agrochemicals, and ligands to transition metals.[1] Showing a wide range of biological activities that have led to the development of many marketed drugs, such as celecoxib, sildenafil, and crizotinib, pyrazole-containing compounds play an important role in medicinal chemistry.[2] In addition, hundreds of new pyrazole-based ligands have been investigated to establish their unique position in organometallic chemistry.[3] Thus, the development of methods for the synthesis of structurally diverse pyrazoles represents an important objective in organic synthesis.[4] The cyclocondensation of carbonyl compounds provides a general approach to pyrazole compounds, but it requires de novo synthetic sequences to be repeated for different substitution patterns using toxic hydrazine reactants. In order to rapidly access a variety of pyrazoles, a cross-coupling reaction can be more useful.[5] In particular, a Suzuki reaction of pyrazolyl halides or pyrazole boronic acid derivatives has broadly been employed. However, a narrow substrate scope along with a significant increase of production cost has been noted.[6] In this regard, a direct substitution at C−H bonds of pyrazoles is an attractive alternative.[7,8] While catalytic C−H functionalization reactions have been dramatically expanded, applications to pyrazoles have been limited largely to arylation reactions along with a single example of alkynylation.[9,10] The catalytic C−H alkylation directly introducing a C(sp^3)-substituent to the pyrazole core has not been reported. Given that installation of alkyl groups to the pyrazole ring provides conformational flexibility, displaying improvement of physical and biological properties,[7a,11] a method for the C-alkylation of pyrazoles that does not depend on the use of a strong base would be highly desirable.

A challenge in the development of catalytic C−H alkylation reactions of pyrazoles is the presence of a Lewis basic nitrogen atom of the heterocyclic ring, which serves as a strong ligand to transition metals. For example, when the N1 atom is substituted with an aryl group, C−H activation takes place at the arene ring rather than the pyrazole ring (Figure 1A).[12] Furthermore, the *N*-alkylation at N2 occurs with alkyl donors like alkyl halides, particularly at high temperatures typically required for many transition-metal-catalyzed C−H activation reactions.[13] Hence, it is expected to be highly difficult to achieve the C−H functionalization of the pyrazole family using activated alkyl halides while avoiding complications from *N*-alkylation.[14−18]

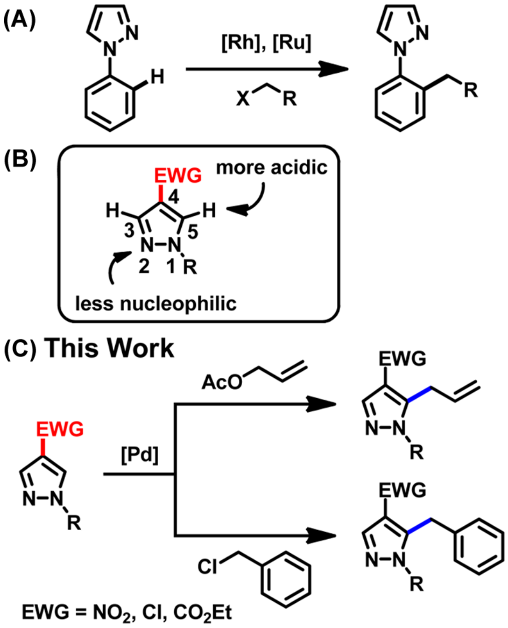


Figure 1. (A) The noninnocent Lewis basic N2 atom of pyrazoles serving as a directing group. (B) The electronic effect of the electron-withdrawing group (EWG). (C) Catalytic C−H allylation and benzylation of pyrazoles containing synthetically useful EWGs.

Our approach to the C−H alkylation of pyrazoles was based on modulation of the pyrazole ring by inductively electron-withdrawing substituents (Figure 1B). We envisioned that the electronic effect rendered by the electron-withdrawing group

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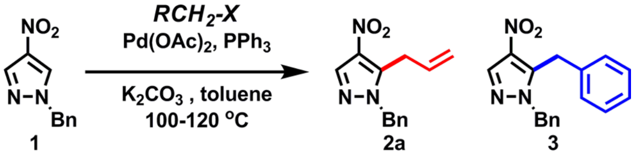
should not only reduce the Lewis basicity of the N2 atom but also enhance the acidity of the C−H bond of pyrazoles, thus enabling a C−H alkylation using activated alkyl halides or pseudohalides. While the effect of the electron-withdrawing group on the C−H functionalization of pyrazoles has been recognized, it has been examined only in the context of the arylation process.[19] Here, we report the first catalytic C−H allylation and benzylation of pyrazoles that occurs with high regioselectivity by taking advantage of synthetically useful electron-withdrawing groups (Figure 1C).[20] Readily available allyl acetates and benzyl chlorides are employed in this reaction as the alkyl donors to provide C5-allylated and benzylated pyrazole compounds in high yields.

At the outset of our study on the alkylation of electron-deficient pyrazole compounds, several factors were considered for the alkyl group source. The activated alkyl halides and pseudohalides should undergo a facile oxidative addition, and be compatible with any nucleophilic reagents (i.e., pyrazoles, phosphines, bases, and solvents). In addition, as the reaction proceeds, the leaving group of alkyl donors can be accumulated to interfere with the catalytic activity of the palladium complex. The initial experiments focusing on the alkyl donors revealed that only allyl acetate and benzyl chloride were suitable for direct C−H allylation and benzylation of nitropyrazole **1**, respectively (Table 1).[21] Other reaction parameters regarding the catalyst system were examined to show the combination of Pd(OAc)$_2$ and PPh$_3$ to be optimal for both allylation and benzylation processes (see the Supporting Information). It was also found that K$_2$CO$_3$ in toluene was sufficient for the allylation and benzylation of the electron-deficient pyrazole **1**, presumably due to the increased acidity of the C−H bond.[22] Notably, no overalkylation at the C3 of the pyrazole ring or at the activated sp^3 carbon of the alkyl chain was observed, and the alkene isomerization of the allyl group was found to be minimal in these reactions (vide infra).[16a,d,g]

Table 1. Effects of the Leaving Group on the C−H Alkylation of 1-Benzyl-4-nitropyrazole[a]



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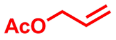
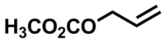
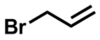
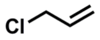
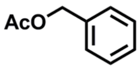
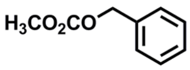
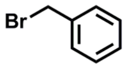
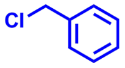
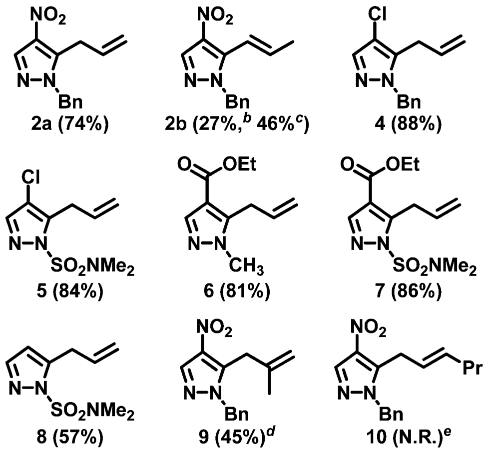
1		2a	74[c]
2		2a	0
3		2a	0
4		2a	0
5		2a	0
6		3	0
7		3	13
8		3	96[c]

[a]Reaction conditions: pyrazole (0.50 mmol), 1.2 equiv of RCH$_2$X, 5.0 mol % of Pd(OAc)$_2$, 20 mol % of PPh$_3$, 2.5 equiv of K$_2$CO$_3$, toluene (0.50 M), 100 °C (benzylation) or 120 °C (allylation), 16−20 h. [b]Isolated yield. [c]In the absence of the Pd catalyst, no desired product was formed.

Under the optimized conditions, the reaction of **1** provided the allylated product **2a** in 74% yield along with a small amount of the isomerization product **2b** (**2a**:**2b** > 20:1) (Table 2). When the reaction was conducted in polar solvent like 1,4-dioxane or subjected to extended heating, the formation of **2b** became prevalent.[23] The C−H allylation was also achieved efficiently with chloro as well as ester substrates to give high yields of allylated pyrazoles **4**, **5**, **6**, and **7**. In these cases, only trace amounts of the corresponding isomerization products were formed based on ^{1}H NMR, possibly due to the weak electron-withdrawing ability of chloro and ester groups compared to the nitro group. The unsubstituted pyrazole protected with a sulfamoyl group afforded the C5-allylated product **8**, which is consistent with the regioselectivity observed in the arylation reaction.[19g] When substituted allylic acetates were employed, the reaction gave 45% yield of **9** and no meaningful amount of **10**.

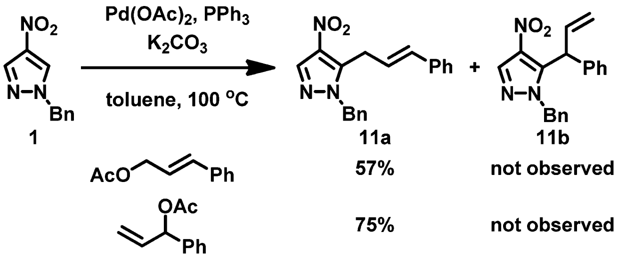
Table 2. Substrate Scope: Allylation[a]



[a]Conditions: pyrazole (0.50 mmol), 1.5 equiv of allyl acetate, 5.0 mol % Pd(OAc)$_2$, 20 mol % PPh$_3$, 2.5 equiv of K$_2$CO$_3$, toluene (0.50 M), 120 °C, 18 h. [b]1,4-Dioxane was used instead of toluene. [c]The reaction mixture in toluene was heated for 4 days. [d]3.0 equiv of K$_2$CO$_3$ was used. [e]N.R. = no reaction.

While significant steric effects on the reactivity of allyl donors were noted, an interesting regioselectivity was observed in the reactions with cinnamyl acetate and the regioisomeric secondary acetate (Scheme 1). Both of them gave rise to the linear isomer **11a** in preference to the branched isomer **11b**,

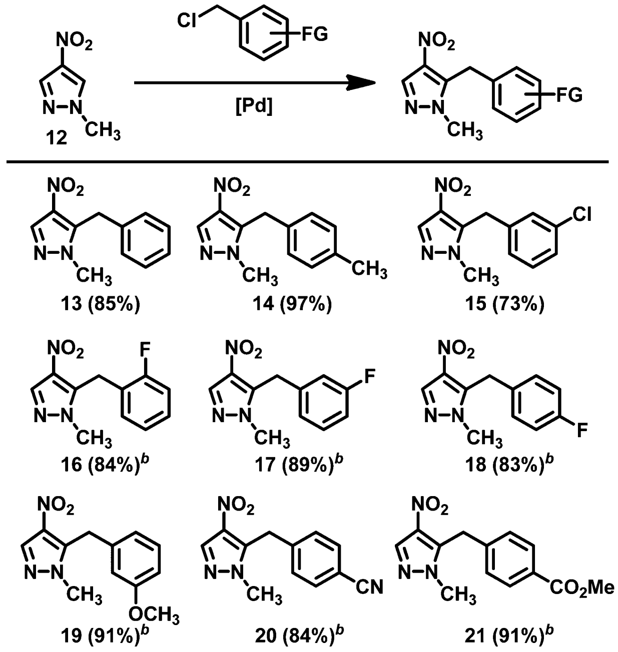
Scheme 1. Regioselectivity of the Allylation



suggesting that the reaction of the allyl palladium species took place only at the less-hindered allylic terminus.

Having demonstrated the feasibility of *N*-benzylpyrazole series, we examined the C−H benzylation of *N*-methylpyrazole substrates. In these reactions, the benzylation was greatly facilitated by the presence of a pivalate anion that was in situ generated in the reaction mixture (for a proposed mechanism, see the Supporting Information).[24] Methylpyrazole **12** was coupled with a wide range of benzyl chlorides to provide **13**−**21** in high yields (Table 3). It was notable that benzyl chlorides possessing substituents of varying electronic and steric properties in the arene ring were well-tolerated.

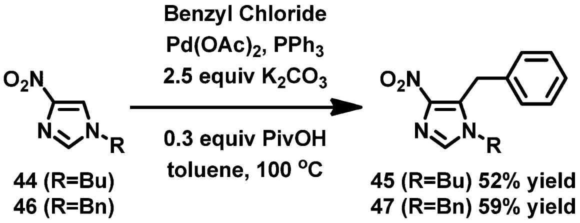
Table 3. Substrate Scope: Benzyl Chlorides[a]



[a]Conditions: pyrazole (0.50 mmol), 1.2 equiv of benzyl chloride, 5.0 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, 2.5 equiv of K_2CO_3, toluene (0.50 M), 100 °C, 18 h. [b]0.30 equiv of PivOH was added.

The substrate scope of the C−H benzylation showed that a variety of pyrazoles could be readily converted to the corresponding benzyl pyrazoles in good to high yields (Table 4). Similar to the allylation, the presence of an electron-withdrawing group (nitro, ester, and chloro groups) at the C4 position proved critical for the benzylation. The palladium system induced the C−H benzylation exclusively on the pyrazole ring rather than the phenyl ring in the reaction of 1-phenyl-4-nitropyrazole **22** (entry 1). Despite the bulkiness of the *N*-protecting group, THP pyrazole **24** was converted to benzylated product **25** in 74% yield (entry 2). The pyrazole with a sulfamoyl *N*-protecting group underwent the benzylation as well (entry 3). The electron-withdrawing sulfamoyl group on the N1 position appeared beneficial to the C−H benzylation, generally leading to higher yields of the corresponding benzylation products than *N*-alkyl-substituted pyrazoles (entries 4 vs 5, 6 vs 8, 7 vs 10). When the chloro group was placed at the C5 position, no C4 benzylation product was formed (entry 11). Also, the sulfamoyl group alone was found to be insufficient for the benzylation (entry 12); the simple sulfamoyl pyrazole **42** did not generate a noticeable amount of C4- or C5-benzylation products.

It was noteworthy that the protocol developed for pyrazoles could be applied to the C−H benzylation of nitroimidazoles despite the higher nucleophilicity of imidazoles than pyrazoles (eq 1). This result indicates that alternative to strong base-mediated benzylation reactions, the direct C−H benzylation of imidazoles can be used when electron-withdrawing groups are present in the imidazole core.[25] However, the current protocol could not be extended to the coupling of secondary benzyl halides or unactivated alkyl halides.[26]



(eq 1)

In conclusion, we have developed a new strategy for the preparation of C5-allyl and benzyl pyrazoles. The electronic character of the pyrazole ring was modulated by the electron-withdrawing effect of the synthetically useful groups, such as nitro, ester, and chloro groups, enabling the C−H allylation and benzylation in an efficient manner. The installation of the sulfamoyl group on the nitrogen atom can further accelerate the benzylation process. In the present allylation and benzylation reactions, the overalkylation of the products does not occur and the alkene isomerization of the allylation products is suppressed. The C−H allylation and benzylation reactions by the Pd complex derived from $Pd(OAc)_2$ and PPh_3 can be carried out under practical laboratory conditions without operational difficulties involving the handling of air- and moisture-sensitive reagents and special equipment to procure cryogenic conditions. This approach, not requiring strong base-promoted reaction conditions, will be useful to provide an expeditious access to allylated and benzylated pyrazoles.

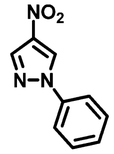
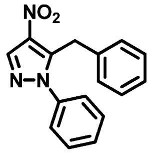
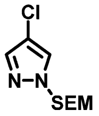
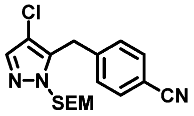
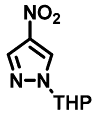
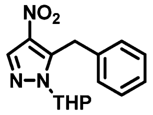
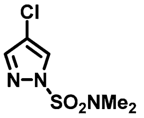
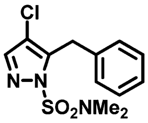
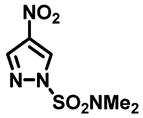
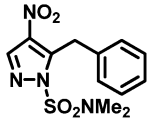
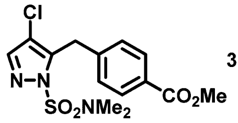
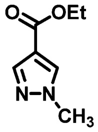
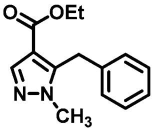
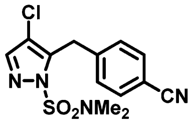
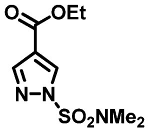
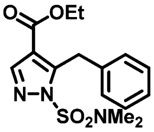
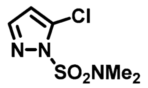
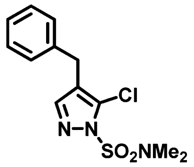
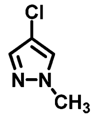
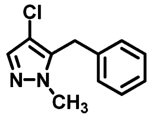
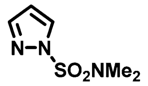
■ EXPERIMENTAL SECTION

All reagents were used as received unless otherwise noted. Flash column chromatography was performed on silica gel (40−63 μm) using the indicated solvent system. Nuclear magnetic resonance spectra were recorded at 300 K on 300 Fourier transform NMR spectrometers in $CDCl_3$. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26). Data for ^1H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad), coupling constant (J) in Hertz, and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$, δ 77.16). Infrared (IR) spectra were reported in frequency of the absorption (cm^{-1}). High-resolution mass spectra (HRMS) were acquired on a high-resolution Q-TOF mass spectrometer (ionization mode: ESI).

1-Benzyl-4-nitro-1*H*-pyrazole (**1**),[19d] 1-benzyl-4-chloro-1*H*-pyrazole,[27] 1-methyl-4-nitro-1*H*-pyrazole (**12**),[19c] 4-nitro-1-phenyl-1*H*-pyrazole (**22**),[28] ethyl 1-methyl-1*H*-pyrazole-4-carboxylate (**28**),[29] 4-chloro-1-methyl-1*H*-pyrazole (**32**),[30] *N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (**42**),[19g] 1-butyl-4-nitro-1*H*-imidazole (**44**),[19d] and 1-benzyl-4-nitro-1*H*-imidazole (**46**)[19d] are known compounds.

General Procedure for the C−H Alkylation of Pyrazoles. To a 8 mL glass vial equipped with a magnetic stir bar were sequentially added K_2CO_3 (173 mg, 1.25 mmol or as indicated), the pyrazole substrate (0.5 mmol), allyl acetate or benzyl chloride (0.6 mmol or as indicated), toluene (1.0 mL, 0.50 M), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and PPh_3 (26.2 mg, 0.1 mmol). The reaction mixture was

Table 4. Substrate Scope: Benzylation[a]

entry	reactant	product	yield	entry	reactant	product	yield
1	 22	 23	87%	7	 34	 35	62%
2	 24	 25	74%	8	 36	 37	81%
3	 26	 27	86%	9	36	 38	84%
4	 28	 29	38%	10	36	 39	77%
5	 30	 31	56%	11	 40	 41	<5%
6	 32	 33	54%	12	 42	 43	<5%

[a]Conditions: pyrazole (0.50 mmol), 1.2 equiv of benzyl chloride, 5.0 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, 2.5 equiv of K_2CO_3, 0.30 equiv of PivOH, toluene (0.50 M), 100 °C, 18 h.

purged with argon through a Teflon-lined cap. Then, the cap was replaced with a new Teflon-lined solid cap. The reaction vial was moved to a preheated reaction block (100 or 120 °C). After stirring for 18 h, the reaction mixture was cooled to 25 °C and concentrated. The residue was purified by flash column chromatography to provide the desired product. For the preparation of compounds **16**, **17**, **18**, **19**, **20**, **21**, **23**, **25**, **27**, **29**, **31**, **33**, **35**, **37**, **38**, **39**, **45**, and **47**, 0.30 equiv of pivalic acid (0.15 mmol) was added.

*5-Allyl-1-benzyl-4-nitro-1H-pyrazole (**2a**).* Purification by flash column chromatography (hexanes/EtOAc = 8:1) provided allylated pyrazole **2a** as a yellow oil (90 mg, 74% yield). IR (film) 3128, 3066, 3033, 2983, 1640, 1552, 1501 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.35−7.33 (m, 3H), 7.16 (d, J = 7.2 Hz, 2H), 5.82−5.70 (m, 1H), 5.32 (s, 2H), 5.12 (d, J = 10.1 Hz, 1H), 5.00 (d, J = 17.1 Hz, 1H), 3.78 (d, J = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 136.6, 134.9, 130.8, 129.1, 128.6, 127.2, 118.2, 54.3, 28.7; HRMS (ESI) calcd for $C_{13}H_{14}N_3O_2$ $[M + H]^+$ 244.1086, found 244.1083.

*(E)-1-Benzyl-4-nitro-5-(prop-1-en-1-yl)-1H-pyrazole (**2b**).* Purification by flash column chromatography (hexanes/EtOAc = 9:1) provided allylated pyrazole **2b** as a yellow oil (33 mg, 27% yield). IR (film) 3033, 2919, 2852, 1659, 1537, 1496 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.37−7.34 (m, 3H), 7.13 (d, J = 7.2 Hz, 2H), 6.60 (d, J = 16.3 Hz, 1H), 6.35−6.25 (m, 1H), 5.38 (s, 2H), 1.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 139.3, 136.9, 135.5, 129.2, 128.4, 126.8, 116.2, 54.6, 19.64; HRMS (ESI) calcd for $C_{13}H_{14}N_3O_2$ $[M + H]^+$ 244.1086, found 244.1083.

*1-Benzyl-4-nitro-1H-pyrazole (**3**).* Purification by flash column chromatography (hexanes/EtOAc = 9:2) provided benzylated pyrazole **3** as a yellow oil (141 mg, 96% yield). IR (film) 3064, 3031, 1552, 1505, 1472, 1455, 1405, 1322 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.35−7.25 (m, 6H), 7.10−7.02 (m, 4H), 5.20 (s, 2H), 4.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 136.7, 135.0, 134.6, 133.7, 129.08, 129.06, 128.5, 128.1, 127.4, 127.2, 54.4, 29.8; HRMS (ESI) calcd for $C_{17}H_{16}N_3O_2$ $[M + H]^+$ 294.1243, found 294.1241.

*5-Allyl-1-benzyl-4-chloro-1H-pyrazole (**4**).* Purification by flash column chromatography (hexanes/EtOAc = 9:1) provided allylated pyrazole **4** as a yellow oil (103 mg, 88% yield). IR (film) 3065, 3032, 2934, 1640, 1455, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.34−7.30 (m, 3H), 7.08 (d, J = 7.1 Hz, 2H), 5.78−5.66 (m, 1H), 5.26 (s, 2H), 5.08 (d, J = 10.0 Hz, 1H), 4.97 (d, J = 17.0 Hz, 1H), 3.33 (d, J = 5.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 136.6, 136.4, 132.2, 128.8, 127.9, 126.9, 126.7, 117.2, 109.4, 54.2, 27.6; HRMS (ESI) calcd for $C_{13}H_{14}ClN_2$ $[M + H]^+$ 233.0846, found 233.0841.

*5-Allyl-4-chloro-N,N-dimethyl-1H-pyrazole-1-sulfonamide (**5**).* Purification by flash column chromatography (hexanes/EtOAc = 8:1) provided allylated pyrazole **5** as a yellow oil (105 mg, 84% yield). IR (film) 3084, 2981, 2944, 1641, 1430, 1385 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 5.95−5.86 (m, 1H), 5.13−5.06 (m, 2H), 3.70 (d, J = 6.1 Hz, 2H), 3.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 140.3, 132.4, 117.4, 112.0, 39.3, 28.4; HRMS (ESI) calcd for $C_8H_{13}ClN_3O_2S$ $[M + H]^+$ 250.0417, found 250.0406.

*Ethyl 5-Allyl-1-methyl-1H-pyrazole-4-carboxylate (**6**).* Purification by flash column chromatography (hexanes/EtOAc = 4:1) provided allylated pyrazole **6** as a yellow oil (79 mg, 81% yield); IR (film) 3082, 2981, 1709, 1640, 1555, 1493, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 5.92−5.79 (m, 1H), 5.11 (dd, J = 10.1, 1.3 Hz, 1H), 4.97 (dd, J = 17.2, 1.3 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.79−3.77 (m, 5H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 144.0, 140.8, 132.7, 116.9, 111.9, 59.9, 36.6, 28.8, 14.5; HRMS (ESI) calcd for $C_{10}H_{15}N_2O_2$ $[M + H]^+$ 195.1134, found 195.1126.

*Ethyl 5-Allyl-1-(N,N-dimethylsulfamoyl)-1H-pyrazole-4-carboxylate (**7**).* Purification by flash column chromatography (hexanes/

EtOAc = 8:1) provided allylated pyrazole **7** as a colorless oil (123 mg, 86% yield). IR (film) 3084, 2983, 2941, 1717, 1563, 1461 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.97 (s, 1H), 6.02−5.89 (m, 1H), 5.16−5.08 (m, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.08 (d, J = 6.2 Hz, 2H), 3.06 (s, 6H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.6, 148.6, 142.9, 133.3, 117.3, 113.6, 60.5, 39.3, 29.0, 14.3; HRMS (ESI) calcd for $C_{11}H_{18}N_3O_4S$ $[M + H]^+$ 288.1018, found 288.1007.

*5-Allyl-N,N-dimethyl-1H-pyrazole-1-sulfonamide (**8**).* Purification by flash column chromatography (hexanes/EtOAc = 7:1) provided allylated pyrazole **8** as a yellow oil (61 mg, 57% yield). IR (film) 3135, 3083, 3013, 2980, 2941, 2857, 1375, 1178 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.56 (s, 1H), 6.13 (d, J = 0.7 Hz, 1H), 6.04−5.89 (m, 1H), 5.22−5.12 (m, 2H), 3.68 (d, J = 6.6 Hz, 2H), 3.02 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.8, 142.0, 133.6, 117.9, 107.4, 39.2, 31.1; HRMS (ESI) calcd for $C_8H_{14}N_3O_2S$ $[M + H]^+$ 216.0807, found 216.0801.

*1-Benzyl-5-(2-methylallyl)-4-nitro-1H-pyrazole (**9**).* Purification by flash column chromatography (hexanes/EtOAc = 9:1) provided allylated pyrazole **9** as a yellow oil (58 mg, 45% yield). IR (film) 2974, 2920, 1552, 1504, 1473, 1406 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.18 (s, 1H), 7.36−7.33 (m, 3H), 7.15 (d, J = 7.6 Hz, 2H), 5.29 (s, 2H), 4.88 (s, 1H), 4.50 (s, 1H), 3.74 (s, 2H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 140.2, 139.6, 136.6, 134.9, 129.1, 128.6, 127.2, 112.9, 54.2, 32.1, 22.7; HRMS (ESI) calcd for $C_{14}H_{16}N_3O_2$ $[M + H]^+$ 258.1243, found 258.1235.

*1-Benzyl-5-cinnamyl-4-nitro-1H-pyrazole (**11a**).* Purification by flash column chromatography (hexanes/EtOAc = 9:1) provided allylated pyrazole **11a** as a yellow solid (91 mg, 57% yield). mp 97−98 °C; IR (film) 3061, 3031, 1550, 1503, 1474, 1449 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.19 (s, 1H), 7.36−7.16 (m, 10H), 6.31 (d, J = 16.0 Hz, 1H), 6.08−5.99 (m, 1H), 5.38 (s, 2H), 3.93 (d, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 140.5, 136.6, 136.3, 135.0, 133.3, 129.2, 128.7, 128.6, 128.0, 127.2, 126.4, 121.9, 54.5, 28.0; HRMS (ESI) calcd for $C_{19}H_{18}N_3O_2$ $[M + H]^+$ 320.1399, found 320.1386.

*5-Benzyl-1-methyl-4-nitro-1H-pyrazole (**13**).* Purification by flash column chromatography (hexanes/EtOAc = 2:1) provided benzylated pyrazole **13** as a white solid (92 mg, 85% yield). mp 59−61 °C; IR (film) 3127, 3087, 3063, 3030, 3005, 2951, 1556, 1504 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.12 (s, 1H), 7.34−7.22 (m, 3H), 7.13 (d, J = 7.4 Hz, 2H), 4.49 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 140.8, 136.2, 134.9, 133.2, 129.1, 128.1, 127.3, 37.7, 30.0; HRMS (ESI) calcd for $C_{11}H_{12}N_3O_2$ $[M + H]^+$ 218.0930, found 218.0932.

*1-Methyl-5-(4-methylbenzyl)-4-nitro-1H-pyrazole (**14**).* Purification by flash column chromatography (hexanes/EtOAc = 3:1) provided benzylated pyrazole **14** as a yellow solid (112 mg, 97% yield). mp 67−69 °C; IR (film) 3128, 3024, 2950, 2923, 1551, 1503, 1401, 1319 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.11 (s, 1H), 7.11 (d, J = 7.6 Hz, 2H), 7.02 (d, J = 7.3 Hz, 2H), 4.44 (s, 2H), 3.76 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 141.1, 137.1, 136.2, 133.2, 131.8, 129.8, 128.0, 37.7, 29.6, 21.1; HRMS (ESI) calcd for $C_{12}H_{14}N_3O_2$ $[M + H]^+$ 232.1086, found 232.1070.

*5-(3-Chlorophenyl)-1-methyl-4-nitro-1H-pyrazole (**15**).* Purification by flash column chromatography (hexanes/EtOAc = 2:1) provided benzylated pyrazole **15** as a yellow solid (92 mg, 73% yield). mp 87−90 °C; IR (film) 3128, 3062, 2951, 1503, 1401, 1319 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.14 (s, 1H), 7.27−7.23 (m, 2H), 7.12 (s, 1H), 7.05−6.98 (m, 1H), 4.47 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 139.9, 136.8, 136.3, 134.9, 133.3, 130.3, 128.2, 127.6, 126.3, 37.7, 29.6; HRMS (ESI) calcd for $C_{11}H_{11}ClN_3O_2$ $[M + H]^+$ 252.0540, found 252.0518.

*5-(2-Fluorobenzyl)-1-methyl-4-nitro-1H-pyrazole (**16**).* Purification by flash column chromatography (hexanes/EtOAc = 2:1) provided benzylated pyrazole **16** as a brown solid (99 mg, 84% yield). mp 92−95 °C; IR (film) 3118, 2958, 2924, 1492, 1456, 1410 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.12 (s, 1H), 7.26−7.25 (m, 1H), 7.12−7.03 (m, 3H), 4.49 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.6 (d, $J_{\text{C-F}}$ = 245.7 Hz), 139.8, 136.3, 133.4, 130.2 (d, $J_{\text{C-F}}$ = 3.7 Hz), 129.3 (d, $J_{\text{C-F}}$ = 8.2 Hz), 124.7 (d, $J_{\text{C-F}}$ = 3.6 Hz), 122.0 (d, $J_{\text{C-F}}$ = 15.0 Hz), 115.7 (d, $J_{\text{C-F}}$ = 21.8 Hz), 37.6 (d, $J_{\text{C-F}}$ = 3.0 Hz), 23.4 (d, $J_{\text{C-F}}$ = 4.0 Hz); HRMS (ESI) calcd for $C_{11}H_{11}FN_3O_2$ $[M + H]^+$ 236.0835, found 236.0813.

*5-(3-Fluorobenzyl)-1-methyl-4-nitro-1H-pyrazole (**17**).* Purification by flash column chromatography (hexanes/EtOAc = 3:1) provided benzylated pyrazole **17** as a yellow solid (105 mg, 89% yield). mp 74−77 °C; IR (film) 3129, 2953, 1504, 1488, 1401, 1317 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.14 (s, 1H), 7.33−7.26 (m, 1H), 7.00−6.81 (m, 3H), 4.49 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 163.2 (d, $J_{\text{C-F}}$ = 247.3 Hz), 140.0, 137.3 (d, $J_{\text{C-F}}$ = 7.4 Hz), 136.3, 133.3, 130.7 (d, $J_{\text{C-F}}$ = 8.4 Hz), 123.8 (d, $J_{\text{C-F}}$ = 3.0 Hz), 115.2 (d, $J_{\text{C-F}}$ = 22.1 Hz), 114.5 (d, $J_{\text{C-F}}$ = 21.0 Hz), 37.7, 29.8; HRMS (ESI) calcd for $C_{11}H_{11}FN_3O_2$ $[M + H]^+$ 236.0835, found 236.0833.

*5-(4-Fluorobenzyl)-1-methyl-4-nitro-1H-pyrazole (**18**).* Purification by flash column chromatography (hexanes/EtOAc = 3:1) provided benzylated pyrazole **18** as a yellow solid (98 mg, 83% yield). mp 74−77 °C; IR (film) 3128, 3045, 2952, 1556, 1504, 1432, 1318, 1224 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.11 (s, 1H), 7.14−7.06 (m, 2H), 7.03−6.95 (m, 2H), 4.44 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.0 (d, $J_{\text{C-F}}$ = 245.3 Hz), 140.6, 136.3, 133.3, 130.6 (d, $J_{\text{C-F}}$ = 3.2 Hz), 129.8 (d, $J_{\text{C-F}}$ = 8.1 Hz), 116.1 (d, $J_{\text{C-F}}$ = 21.6 Hz), 37.7, 29.3; HRMS (ESI) calcd for $C_{11}H_{11}FN_3O_2$ $[M + H]^+$ 236.0835, found 236.0815.

*5-(3-Methoxybenzyl)-1-methyl-4-nitro-1H-pyrazole (**19**).* Purification by flash column chromatography (hexanes/EtOAc = 3:2) provided benzylated pyrazole **19** as a yellow solid (113 mg, 91% yield). mp 74−77 °C; IR (film) 3127, 3054, 3003, 2949, 2837, 1504, 1403, 1316 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.12 (s, 1H), 7.25−7.19 (m, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.72−6.66 (m, 2H), 4.46 (s, 2H), 3.772 (s, 3H), 3.766 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.1, 140.6, 136.4, 136.2, 133.2, 130.1, 120.4, 114.3, 112.3, 55.3, 37.7, 30.0; HRMS (ESI) calcd for $C_{12}H_{14}N_3O_3$ $[M + H]^+$ 248.1035, found 248.1038.

*4-((1-Methyl-4-nitro-1H-pyrazole-5-yl)methyl)benzonitrile (**20**).* Purification by flash column chromatography (hexanes/EtOAc = 2:1) provided benzylated pyrazole **20** as a yellow solid (102 mg, 84% yield). mp 118−121 °C; IR (film) 3139, 3122, 2958, 2228, 1552, 1504, 1410, 1320 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.15 (s, 1H), 7.62 (d, J = 7.5 Hz, 2H), 7.26−7.21 (m, 2H), 4.54 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 140.4, 139.2, 136.3, 133.4, 132.8, 128.9, 118.4, 111.4, 37.7, 30.1; HRMS (ESI) calcd for $C_{12}H_{11}N_4O_2$ $[M + H]^+$ 243.0882, found 243.0870.

*Methyl 4-((1-Methyl-4-nitro-1H-pyrazol-5-yl)methyl)benzoate (**21**).* Purification by flash column chromatography (hexanes/EtOAc = 2:1) provided benzylated pyrazole **21** as a yellow oil (125 mg, 91% yield). IR (film) 3128, 2999, 2953, 2847, 1716, 1504 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.13 (s, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.53 (s, 2H), 3.89 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.5, 140.0, 139.9, 136.3, 133.3, 130.3, 129.3, 128.1, 52.2, 37.7, 30.0; HRMS (ESI) calcd for $C_{13}H_{14}N_3O_4$ $[M + H]^+$ 276.0984, found 276.0982.

*5-Benzyl-4-nitro-1-phenyl-1H-pyrazole (**23**).* Purification by flash column chromatography (hexanes/EtOAc = 7:1) provided benzylated pyrazole **23** as a yellow oil (122 mg, 87% yield). IR (film) 3126, 3063, 3030, 2925, 1548, 1504, 1404, 1323 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.34 (s, 1H), 7.52−7.44 (m, 3H), 7.32−7.27 (m, 2H), 7.25−7.20 (m, 3H), 6.99−6.92 (m, 2H), 4.45 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 141.6, 137.9, 137.3, 135.8, 134.0, 129.9, 129.5, 128.8, 128.0, 127.1, 126.0, 30.6; HRMS (ESI) calcd for $C_{16}H_{14}N_3O_2$ $[M + H]^+$ 280.1086, found 280.1076.

*4-Nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole (**24**).* To a stirred solution of 4-nitropyrazole (2.00 g, 17.7 mmol) in THF (6.0 mL) at 25 °C were added 3,4-dihydro-2*H*-pyran (4.84 mL, 53.1 mmol) and *p*-toluenesulfonic acid monohydrate (167 mg, 0.878 mmol). After stirring for 16 h at 25 °C, the reaction mixture was treated with water (15 mL) and EtOAc (20 mL) and transferred to a 125 mL separatory funnel. The organic layer was collected, and the aqueous layer was extracted with EtOAc (25 mL × 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/EtOAc = 2:1) to provide pyrazole **24** as a yellow oil (3.12 g, 89% yield). IR (film) 3131, 2947, 2864, 1511, 1410, 1308 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.09 (s, 1H), 5.41 (d, J = 9.1 Hz, 1H), 4.08 (d, J = 11.0 Hz, 1H), 3.78−3.68 (m, 1H), 2.17 (d, J = 10.3 Hz, 1H), 2.07−1.90 (m, 2H), 1.80−1.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 127.1, 88.5, 67.9, 30.7, 24.8, 21.7; HRMS (ESI) calcd for $C_8H_{12}N_3O_3$ [M + H]$^+$ 198.0879, found 198.0869.

5-Benzyl-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole (**25**). Purification by flash column chromatography (hexanes/EtOAc = 9:2) provided benzylated pyrazole **25** as a yellow oil (106 mg, 74% yield). IR (film) 3030, 2944, 2856, 1505, 1409, 1317 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.32−7.20 (m, 3H), 7.13 (d, J = 7.3 Hz, 2H), 5.26 (d, J = 9.2 Hz, 1H), 4.76 (d, J = 15.8 Hz, 1H), 4.36 (d, J = 15.8 Hz, 1H), 3.96 (d, J = 11.6 Hz, 1H), 3.54 (t, J = 10.8 Hz, 1H), 2.40−2.27 (m, 1H), 2.08−2.01 (dd, J = 9.1, 3.9 Hz, 1H), 1.78 (d, J = 13.2 Hz, 1H), 1.64−1.47 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 136.4, 135.5, 133.8, 129.0, 128.2, 127.3, 85.4, 67.8, 29.7, 28.9, 24.7, 22.2; HRMS (ESI) calcd for $C_{15}H_{18}N_3O_3$ [M + H]$^+$ 288.1348, found 288.1349.

N,N-Dimethyl-4-nitro-1H-pyrazole-1-sulfonamide (**26**). To a stirred solution of 4-nitropyrazole (1.00 g, 8.84 mmol) in THF (10.0 mL) at 25 °C were added K_2CO_3 (1.83 g, 13.3 mmol) and dimethylsulfamoyl chloride (0.95 mL, 8.84 mmol). After stirring for 19 h at 25 °C, the reaction mixture was treated with water (15 mL) and EtOAc (20 mL) and transferred to a 250 mL separatory funnel. The organic layer was collected, and the aqueous layer was extracted with EtOAc (25 mL × 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by crystallization (EtOAc/hexanes) to provide pyrazole **26** as a white solid (1.43 g, 74% yield). mp 91−93 °C; IR (film) 3143, 3129, 3114, 1537, 1421, 1399, 1305, 1201 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.23 (s, 1H), 3.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 136.2, 130.3, 39.0; HRMS (FAB) calcd for $C_5H_9N_4O_4S$ [M + H]$^+$ 221.0345, found 221.0343.

5-Benzyl-N,N-dimethyl-4-nitro-1H-pyrazole-1-sulfonamide (**27**). Purification by flash column chromatography (hexanes/EtOAc = 9:1) provided benzylated pyrazole **27** as a yellow solid (134 mg, 86% yield). mp 85−88 °C; IR (film) 3129, 3064, 3032, 2949, 1552, 1514, 1399, 1319 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.32−7.22 (m, 5H), 4.79 (s, 2H), 3.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 137.8, 135.6, 134.0, 128.8, 128.7, 127.2, 39.4, 30.1; HRMS (ESI) calcd for $C_{12}H_{15}N_4O_4S$ [M + H]$^+$ 311.0814, found 311.0798.

Ethyl 5-Benzyl-1-methyl-1H-pyrazole-4-carboxylate (**29**). Purification by flash column chromatography (hexanes/EtOAc = 3:1) provided benzylated pyrazole **29** as a yellow oil (46 mg, 38% yield). IR (film) 2981, 1708, 1555, 1495, 1444, 1408, 1377, 1241 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.32−7.17 (m, 3H), 7.12 (d, J = 7.3 Hz, 2H), 4.42 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.70 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 144.8, 140.9, 136.7, 128.9, 128.2, 126.8, 112.5, 60.0, 36.9, 30.2, 14.5; HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2$ [M + H]$^+$ 245.1290, found 245.1289.

Ethyl 1-(N,N-Dimethylsulfamoyl)-1H-pyrazole-4-carboxylate (**30**). To a stirred solution of ethyl 1*H*-pyrazole-4-carboxylate (1.00 g, 7.14 mmol) in THF (10.0 mL) at 0 °C under a nitrogen atmosphere was added sodium hydride 60% in oil (343 mg, 8.56 mmol). After stirring for 20 min at 0 °C, dimethylsulfamoyl chloride (0.77 mL, 7.14 mmol) was added dropwise, and then the mixture was stirred for 22 h at 25 °C. The reaction mixture was treated with water (15 mL) and EtOAc (20 mL) and transferred to a 250 mL separatory funnel. The organic layer was collected, and the aqueous layer was extracted with EtOAc (25 mL × 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/EtOAc = 4:1) to provide pyrazole **30** as a colorless oil (1.61 g, 91% yield). IR (film) 3143, 2983, 2941, 1716, 1557, 1392, 1342, 1246 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.91 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 2.80 (s, 6H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 143.7, 134.5, 116.0, 60.6, 38.5, 14.1; HRMS (ESI) calcd for $C_8H_{14}N_3O_4S$ [M + H]$^+$ 248.0705, found 248.0705.

Ethyl 5-Benzyl-1-(N,N-dimethylsulfamoyl)-1H-pyrazole-4-carboxylate (**31**). Purification by flash column chromatography (hexanes/EtOAc = 4:1) provided benzylated pyrazole **31** as a yellow oil (94 mg, 56% yield). IR (film) 3088, 3064, 3031, 2982, 2941, 1716, 1384, 1261 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.28−7.16 (m, 5H), 4.72 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 2.86 (s, 6H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 149.2, 143.2, 137.4, 128.7, 128.4, 126.6, 114.3, 60.7, 39.0, 30.3, 14.4; HRMS (ESI) calcd for $C_{15}H_{20}N_3O_4S$ [M + H]$^+$ 338.1175, found 338.1174.

5-Benzyl-4-chloro-1-methyl-1H-pyrazole (**33**). Purification by flash column chromatography (hexanes/EtOAc = 6:1) provided benzylated pyrazole **33** as a colorless oil (56 mg, 54% yield). IR (film) 3063, 3029, 2944, 1604, 1544, 1419 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.33−7.23 (m, 3H), 7.12 (d, J = 7.9 Hz, 2H), 4.03 (s, 2H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 136.5, 136.4, 128.9, 128.1, 126.9, 109.2, 37.7, 29.3; HRMS (ESI) calcd for $C_{11}H_{12}ClN_2$ [M + H]$^+$ 207.0689, found 207.0688.

4-Chloro-1-((2-trimethylsilyl)ethoxy)methyl)-1H-pyrazole (**34**). To a stirred solution of 4-chloropyrazole (2.47 g, 24.1 mmol) in THF (20.0 mL) at 0 °C under a nitrogen atmosphere was added sodium hydride 60% in oil (1.45 g, 36.1 mmol). After stirring for 20 min at 0 °C, 2-(chloromethoxy)ethyl-trimethylsilane (4.27 mL, 24.1 mmol) was added dropwise, and then the mixture was stirred for 22 h at 25 °C. The reaction mixture was treated with water (15 mL) and EtOAc (20 mL) and transferred to a 250 mL separatory funnel. The organic layer was collected, and the aqueous layer was extracted with EtOAc (25 mL × 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/EtOAc = 9:1) to provide pyrazole **34** as a colorless liquid (5.46 g, 97% yield). IR (film) 3125, 2954, 2897, 1453, 1431, 1374, 1312, 1250 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.46 (s, 1H), 5.37 (s, 2H), 3.54 (t, J = 8.3 Hz, 2H), 0.90 (t, J = 8.3 Hz, 2H), 6.71 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 127.3, 111.4, 80.9, 67.0, 17.8, −1.4; HRMS (ESI) calcd for $C_9H_{18}ClN_2OSi$ [M + H]$^+$ 233.0877, found 233.0869.

4-((4-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-5-yl)methyl)benzonitrile (**35**). Purification by flash column chromatography (hexanes/EtOAc = 10:1) provided benzylated pyrazole **35** as a colorless oil (108 mg, 62% yield). IR (film) 3117, 3053, 2953, 2896, 2229, 1368, 1309, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.1 Hz, 2H), 7.48 (s, 1H), 7.31−7.26 (m, 2H), 5.27 (s, 2H), 4.17 (s, 2H), 3.41 (t, J = 8.4 Hz, 2H), 0.74 (t, J = 8.4 Hz, 2H), −0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 137.2, 136.6, 132.3, 128.9, 118.5, 110.9, 110.7, 79.2, 66.3, 28.9, 17.4, −1.6; HRMS (EI) calcd for $C_{17}H_{22}ClN_3OSi$ [M]$^+$ 347.1221, found 347.1219.

4-Chloro-N,N-dimethyl-1H-pyrazole-1-sulfonamide (**36**). To a stirred solution of 4-chloropyrazole (1.00 g, 9.75 mmol) in THF (10.0 mL) at 0 °C under a nitrogen atmosphere was added sodium hydride 60% in oil (0.507 g, 12.7 mmol). After stirring for 20 min at 0 °C, dimethylsulfamoyl chloride (1.15 mL, 10.7 mmol) was added dropwise, and then the mixture was stirred for 16 h at 25 °C. The reaction mixture was treated with water (15 mL) and EtOAc (20 mL) and transferred to a 250 mL separatory funnel. The organic layer was collected, and the aqueous layer was extracted with EtOAc (25 mL × 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/EtOAc = 3:1) to provide pyrazole **36** as a white solid (1.78 g, 87% yield). mp 42−44 °C; IR (film) 3143, 3115, 2947, 1474, 1458, 1420 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.65 (s, 1H), 2.96 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 129.2, 110.4, 38.9; HRMS (ESI) calcd for $C_5H_9ClN_3O_2S$ [M + H]$^+$ 210.0104, found 210.0101.

5-Benzyl-4-chloro-N,N-dimethyl-1H-pyrazole-1-sulfonamide (**37**). Purification by flash column chromatography (hexanes/EtOAc = 8:1) provided benzylated pyrazole **37** as a colorless oil (122 mg, 81% yield). IR (film) 3064, 3031, 2975, 2930, 1455, 1384 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.33−7.15 (m, 5H), 4.32 (s, 2H), 2.83 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 140.5, 137.0, 128.7, 128.6, 126.9, 112.6, 39.0, 29.9; HRMS (ESI) calcd for $C_{12}H_{15}ClN_3O_2S$ $[M + H]^+$ 300.0574, found 300.0576.

*Methyl 4-((4-Chloro-1-(N,N-dimethylsulfamoyl)-1H-pyrazol-5-yl)-methyl)benzoate (**38**).* Purification by flash column chromatography (hexanes/EtOAc = 7:1) provided benzylated pyrazole **38** as a colorless oil (150 mg, 84% yield). IR (film) 2952, 1722, 1612, 1435, 1417, 1386, 1316 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, $J = 8.1$ Hz, 2H), 7.64 (s, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 4.37 (s, 2H), 3.89 (s, 3H), 2.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 142.2, 140.6, 140.4, 129.8, 128.7, 128.5, 112.7, 52.1, 39.0, 29.8; HRMS (ESI) calcd for $C_{14}H_{17}ClN_3O_4S$ $[M + H]^+$ 358.0628, found 358.0627.

*4-Chloro-5-(4-cyanobenzyl)-N,N-dimethyl-1H-pyrazole-1-sulfonamide (**39**).* Purification by flash column chromatography (hexanes/EtOAc = 4:1) provided benzylated pyrazole **39** as a white solid (125 mg, 77% yield). mp 94−97 °C; IR (film) 2926, 2360, 2342, 2229, 1608, 1384 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.58 (d, $J = 8.2$ Hz, 2H), 7.35 (d, $J = 7.7$ Hz, 2H), 4.36 (s, 2H), 2.92 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 140.4, 139.8, 132.4, 129.3, 118.8, 112.9, 110.7, 39.1, 29.9; HRMS (ESI) calcd for $C_{13}H_{14}ClN_4O_2S$ $[M + H]^+$ 325.0526, found 325.0523.

*5-Benzyl-1-butyl-4-nitro-1H-imidazole (**45**).* Purification by flash column chromatography (hexanes/EtOAc = 2:3) provided benzylated imidazole **45** as a yellow solid (68 mg, 52% yield). mp 81−84 °C; IR (film) 2960, 2933, 2874, 1495, 1350, 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.32−7.20 (m, 3H), 7.11 (d, $J = 6.7$ Hz, 2H), 4.49 (s, 2H), 3.79 (t, $J = 7.5$ Hz, 2H), 1.60−1.50 (m, 2H), 1.28−1.20 (m, 2H), 0.84 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 135.8, 134.9, 131.8, 129.1, 128.0, 127.3, 45.9, 32.2, 29.8, 19.7, 13.5; HRMS (ESI) calcd for $C_{14}H_{18}N_3O_2$ $[M + H]^+$ 260.1399, found 260.1393.

*1,5-Dibenzyl-4-nitro-1H-imidazole (**47**).* Purification by flash column chromatography (hexanes/EtOAc = 1:1) provided imidazole **47** as a yellow solid (87 mg, 59% yield). mp 98−99 °C; IR (film) 3112, 3063, 3031, 2925, 2853, 1495, 1352, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.38−7.31 (m, 3H), 7.31−7.20 (m, 3H), 7.08 (d, $J = 6.9$ Hz, 2H), 7.04−6.94 (m, 2H), 4.98 (s, 2H), 4.40 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 135.5, 135.4, 133.6, 132.1, 129.4, 129.1, 128.9, 128.1, 127.3, 127.1, 49.7, 29.7; HRMS (ESI) calcd for $C_{17}H_{16}N_3O_2$ $[M + H]^+$ 294.1243, found 294.1240.

■ ASSOCIATED CONTENT

Supporting Information

Optimization study results, proposed mechanism, and ^1H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Yet. L. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, U.K., 2008; Vol. 4, pp 1−141.

(2) Pérez-Fernández, R.; Goya, P.; Elguero, J. *ARKIVOC* **2014**, 233.

(3) (a) Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943. (b) Mukherjee, R. *Coord. Chem. Rev.* **2000**, *203*, 151.

(4) For reviews, see: (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (b) Janin, Y. L. *Chem. Rev.* **2012**, *112*, 3924.

(5) Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283.

(6) Crizotinib: de Koning, P. D.; McAndrew, D.; Moore, R.; Moses, I. B.; Boyles, D. C.; Kissick, K.; Stanchina, C. L.; Cuthbertson, T.; Kamatani, A.; Rahman, L.; Rodriguez, R.; Urbina, A.; Sandoval, A.; Rose, P. R. *Org. Process Res. Dev.* **2011**, *15*, 1018.

(7) For examples of benzylation reactions of lithiated pyrazoles, see: (a) Velankar, A. D.; Quintini, G.; Prabhu, A.; Weber, A.; Hunaeus, G.; Voland, B.; Wuest, M.; Orjeda, C.; Harel, D.; Varghese, S.; Gore, V.; Patil, M.; Gayke, D.; Herdemann, M.; Heit, I.; Zaliani, A. *Bioorg. Med. Chem.* **2010**, *18*, 4547. (b) Subramanyam, C. *Synth. Commun.* **1995**, *25*, 761.

(8) For examples of allylation reactions of metallated pyrazoles, see: (a) Despotopoulou, C.; Klier, L.; Knochel, P. *Org. Lett.* **2009**, *11*, 3326. (b) Moss, T. A. *Tetrahedron Lett.* **2013**, *54*, 4254.

(9) For direct arylation reactions of pyrazoles, see: (a) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042. (b) Choi, Y. L.; Lee, H.; Kim, B. T.; Choi, K.; Heo, J.-N. *Adv. Synth. Catal.* **2010**, *352*, 2041. (c) Beladhria, A.; Beydoun, K.; Ben Ammar, H.; Ben Salem, R.; Doucet, H. *Synthesis* **2011**, 2553. (d) Bellina, F.; Lessi, M.; Manzai, C. *Eur. J. Org. Chem.* **2013**, 5621.

(10) For direct alkynylation of pyrazoles, see: Jie, X.; Shang, Y.; Hu, P.; Su, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 3630.

(11) (a) Nakai, T.; Perl, N. R.; Moore, J. WO 2014/047325, 2014. (b) Zhang, H.; Ryono, D. E.; Devasthale, P.; Wang, W.; O'Malley, K.; Farrelly, D.; Gu, L.; Harrity, T.; Cap, M.; Chu, C.; Locke, K.; Zhang, L.; Lippy, J.; Kunselman, L.; Morgan, N.; Flynn, N.; Moore, L.; Hosagrahara, V.; Zhang, L.; Kadiyala, P.; Xu, C.; Doweyko, A. M.; Bell, A.; Chang, C.; Muckelbauer, J.; Zahler, R.; Hariharan, N.; Cheng, P. T. W. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1451. (c) Almansa, C.; Gómez, L. A.; Cavalcanti, F. L.; de Arriba, A. F.; García-Rafanell, J.; Form, J. *J. Med. Chem.* **1997**, *40*, 547.

(12) For examples of pyrazole-directed C−H alkylation reactions of arenes, see: (a) Wang, H.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5386. (b) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966. (c) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045.

(13) Schmidt, A.; Dreger, A. *Curr. Org. Chem.* **2011**, *15*, 2897.

(14) For examples of the catalytic C−H alkylation of azoles using unactivated alkyl halides, see: (a) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061. (b) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 12307. (c) Ackermann, L.; Punji, B.; Song, W. F. *Adv. Synth. Catal.* **2011**, *353*, 3325. (d) Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. *Org. Lett.* **2012**, *14*, 1748.

(15) For an example of the C−H allylation of azoles, see: Makida, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4122.

(16) For examples of the catalytic C−H benzylation of azoles, see: (a) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160. (b) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647. (c) Ackermann, L.; Barfüesser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724. (d) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360. (e) Ackermann, L.; Barfüesser, S.; Kornhaass, C.; Kapdi, A. R. *Org. Lett.* **2011**, *13*, 3082. (f) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *ChemCatChem* **2011**, *3*, 893. (g) Xie, P.; Huang, H.; Xie, Y.; Guo, S.; Xia, C. *Adv. Synth. Catal.* **2012**, *354*, 1692. (h) Campbell, A. N.; Cole, K. P.; Martinelli, J. R.; May, S. A.; Mitchell, D.; Pollock, P. M.; Sullivan, K. A. *Org. Process Res. Dev.* **2013**, *17*, 273.

(17) For an example of direct allylation and benzylation of oxazoles and thiazoles using *N*-tosylhydrazones, see: Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296.

(18) For recent sp^2 C−H functionalization reactions using activated alkyl halides and pseudohalides, see: (a) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158. (b) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. (c) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2990. (d) Fan, S.; Chen, F.; Zhang, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 5918. (e) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (f) Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755. (g) Kim, M.; Sharma, S.; Mishra, N. K.; Han, S.; Park, J.; Kim, M.; Shin, Y.; Kwak, J. H.; Han, S. H.; Kim, I. S. *Chem. Commun.* **2014**, *50*, 11303.

(19) Cl: (a) Mateos, C.; Mendiola, J.; Carpintero, M.; Mínguez, J. M. *Org. Lett.* **2010**, *12*, 4924. (b) Yan, T.; Chen, L.; Bruneau, C.; Dixneuf, P. H.; Doucet, H. *J. Org. Chem.* **2012**, *77*, 7659. NO_2: (c) Iaroshenko, V. O.; Gevorgyan, A.; Davydova, O.; Villinger, A.; Langer, P. *J. Org. Chem.* **2014**, *79*, 2906. (d) Jung, H.; Bae, S.; Jang, H.-L.; Joo, J. M. *Bull. Korean Chem. Soc.* **2014**, *35*, 3009. CHO: (e) Smari, I.; Youssef, C.; Yuan, K.; Beladhria, A.; Amman, H. B.; Hassine, B. B.; Doucet, H. *Eur. J. Org. Chem.* **2014**, 1778. CF_3: (f) Gaulier, S. M.; McKay, R.; Swain, N. A. *Tetrahedron Lett.* **2011**, *52*, 6000. *N*-SO_2NMe_2: (g) Kumpulainen, E. T. T.; Pohjakallio, A. *Adv. Synth. Catal.* **2014**, *356*, 1555.

(20) The Claisen rearrangement of allyl ethers and allylsulfonium salts afforded the corresponding allylated pyrazoles. (a) Ichikawa, H.; Watanabe, R.; Fujino, Y.; Usami, Y. *Tetrahedron Lett.* **2011**, *52*, 4448. (b) Eberhart, A. J.; Cicoira, C.; Procter, D. J. *Org. Lett.* **2013**, *15*, 3994.

(21) The reaction with allyl chloride provided the allylation product **8** in 40% yield along with the olefin isomerization product in 10% yield when PPh_3 was absent. The inhibitory effect of the phosphine ligand in the allylation of polyfluoroarenes with allyl chlorides has been noted. Yu, Y.-B.; Fan, S.; Zhang, X. *Chem.—Eur. J.* **2012**, *18*, 14643.

(22) While both C−H bonds at C3 and C5 positions are activated by the electron-withdrawing group, the C−H bond at C3 is disfavored due to the destabilization by electronic repulsion between the developing C−Pd bond and lone pair of N2. (a) Joo, J. M.; Touré, B. B.; Sames, D. *J. Org. Chem.* **2010**, *75*, 4911. (b) Petit, A.; Flygare, J.; Miller, A. T.; Winkel, G.; Ess, D. H. *Org. Lett.* **2012**, *14*, 3680.

(23) Several mechanistic scenarios can be considered to account for the isomerization: (1) base-promoted isomerization, (2) electrophilic palladation, followed by hydrogen transfer, and (3) 1,3-hydrogen shift enabled by Pd hydride complexes. (a) Kim, S. H.; Kim, S. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2010**, *51*, 2774. (b) Sen, A.; Lai, T.-W. *Inorg. Chem.* **1984**, *23*, 3257. (c) Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. *J. Am. Chem. Soc.* **2010**, *132*, 7998. (d) Lim, H. J.; Smith, C. R.; RajanBabu, T. V. *J. Org. Chem.* **2009**, *74*, 4565.

(24) (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (c) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.

(25) Wijtmans, M.; Celanire, S.; Snip, E.; Gillard, M. R.; Gelens, E.; Collart, P. P.; Venhuis, B. J.; Christophe, B.; Hulscher, S.; van der Goot, H.; Lebon, F.; Timmerman, H.; Bakker, R. A.; Lallemand, B. I. L. F.; Leurs, R.; Talaga, P. E.; de Esch, I. J. P. *J. Med. Chem.* **2008**, *51*, 2944.

(26) Kambe, N.; Iwasakia, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937.

(27) Begtrup, M. *Acta Chem. Scand.* **1973**, *27*, 3101.

(28) Jędrysiak, R.; Sawicki, M.; Wagner, P.; Suwiński, J. *ARKIVOC* **2007**, 103.

(29) Holzer, W.; Seiringer, G. *J. Heterocycl. Chem.* **1993**, *30*, 865.

(30) Zhao, Z.-G.; Wang, Z.-X. *Synth. Commun.* **2007**, *37*, 137.