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Pd-catalyzed cross-coupling reactions of halogenated 1-phenylpyrazol-3-ols and related triflates

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ABSTRACT

1-Phenyl-1*H*-pyrazol-3-ol was used as a versatile synthon for the preparation of various 1-phenyl-1*H*-pyrazole derivatives substituted at C-3 and C-4 of the pyrazole nucleus and at the phenyl ring *para*-position. Treatment of 1-phenyl-1*H*-pyrazol-3-ol with triflic anhydride in the presence of base gave 3-trifloyloxy pyrazole, while bromination and iodination yielded the corresponding halogenated derivatives. The obtained scaffolds were used in carbon–carbon bond forming Pd-catalyzed cross-coupling reactions to yield (het)aryl- and carbo-functionally substituted 1-phenyl-1*H*-pyrazoles.

1. Introduction

Pyrazoles are common motifs in material,[1] agricultural,[2] and pharmaceutical[3] sciences. More specifically, 1-phenylpyrazole derivatives are known to have a broad spectrum of biological activities. For example, 4-amino-*N*-(1-phenyl-1*H*-pyrazol-5-yl)benzensulfonamide (Sulfaphenazole) derived from 5-amino-1-phenylpyrazole is a potent antibacterial drug,[4] while 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (CDPPD) has been identified as a positive allosteric metabotropic modulator of the glutamate receptor.[5] Nonsteroidal anti-inflammatory drugs such as Lonazolac are (1,3-diphenyl-1*H*-pyrazol-4-yl)acetic acid derivatives (Fig. 1).[6] The anti-inflammatory activity is also characteristic of (1,4-diphenylpyrazol-3-yl)acetic, -propionic, and -butyric acids.[7] The widely prescribed COX-2 inhibitor Celecoxib carries a trifluoromethyl substituent at the C-3 of the pyrazole nucleus and a partial sulfonamide structure at the *N*-phenyl ring.[8] 1,3-Diphenylpyrazoles containing heterocyclic moieties such as pyrimidine, 1,3,4-oxadiazole or 1,2,4-triazole at the C-4 have been tested for their antimicrobial, antifungal, and antiviral activities.[9] 4-Alkyl-1,2,5-tris(4-hydroxyphenyl)pyrazoles have been studied as estrogen receptor-selective agonists.[10]

Many methods have been described in the literature for the synthesis of substituted 1-phenylpyrazoles. The most common approach is based on the cyclocondensation of *N*-arylhydrazines with 1,3-dicarbonyl compounds; unfortunately, asymmetric 1,3-diketones often give a mixture of two regioisomers.[11] An alternative method is the catalyzed N-arylation of the 1*H*-pyrazole unit.[12] However, in the case of unsymmetrical pyrazoles, this route faces a similar problem of regioselectivity because pyrazole can act as an ambident nucleophile due to tautomerism.[13]

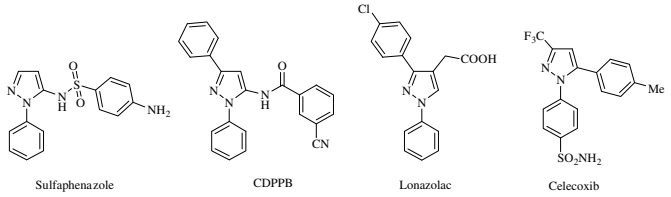

Figure 1. Some pharmaceuticals bearing the *N*-phenylpyrazole moiety.

In order to develop an efficient synthetic approach to the various 3- and 4-substituted 1-phenyl-1*H*-pyrazoles, we chose to explore the palladium-catalyzed coupling reactions for incorporating the desired substituents to the fully assembled core. There have been several literature reports on the palladium-catalyzed cross-coupling reactions of halo- and pseudohalo-substituted pyrazoles. Most of these studies report the Suzuki cross-couplings of 4(5)-bromo-, 4(5)-iodo or 5-trifloyloxy-1*H*-pyrazoles with arylboronic acids,[14] and, correspondingly, 4(5)-(1,3,2-dioxaborolan-2-yl)-1*H*-pyrazoles or 4(5)-pyrazoleboronic acids with haloarenes.[15] Collins et al. utilized a Suzuki cross-coupling of 3(5)-pyrazolyl nonaflates for regioselective synthesis of 3,5-diaryl-1-methyl-1*H*-pyrazoles.[16] Wang et al. performed Suzuki, Sonogashira, and Stille cross-couplings on 1-aryl-5-bromo-1*H*-pyrazoles for the preparation of 1-aryl-1*H*-pyrazoles substituted at the C-5 position.[17]

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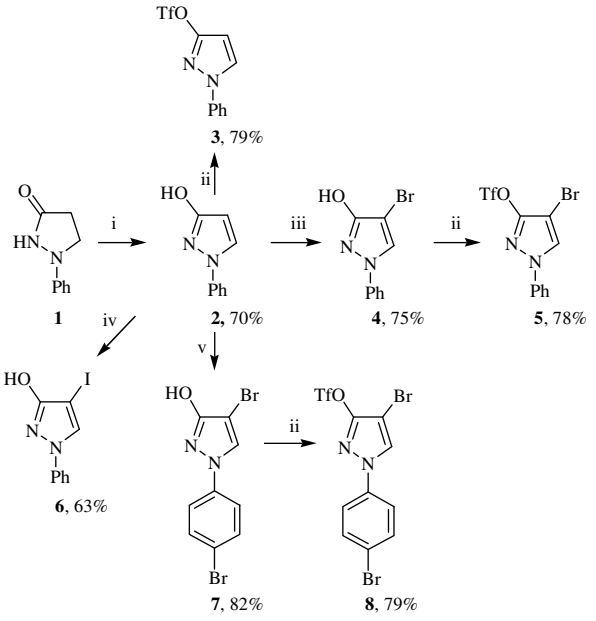
A survey of the literature has shown that Pd-catalyzed cross-coupling reactions remain one of the most efficient methods for the functionalization of 1*H*-pyrazoles. Although this method has found many applications in synthesizing novel pyrazoles, there is still a great deal of work remaining to enable the development of efficient protocols for structurally different compounds and to make these reactions more practical by using inexpensive and easily available starting materials.

2. Results and discussion

We chose 1-phenylpyrazol-3-ol (**2**) as a starting material for the synthesis of 3- and 4-substituted 1-phenyl-1*H*-pyrazoles. Compound **2** was obtained by oxidation of the commercially available 1-phenylpyrazolidin-3-one (**1**) according to a previously described method.[18] The second step in our synthetic sequence was the preparation of substrates suitable for Pd-catalyzed cross-coupling reactions by introducing substituents such as halogen atoms and the triflic group into the pyrazole core.

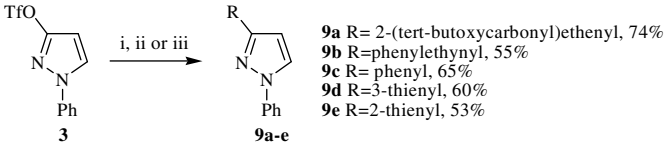
The general method for the preparation of *O*-triflates is treatment of hydroxylic substrates with triflic anhydride in the presence of non-nucleophilic tertiary amines or inorganic bases.[14c,d,19] We easily introduced the triflate group at C-3 of the pyrazole nucleus by reaction of compound **2** with triflic anhydride in the presence of triethylamine in methylene chloride to give the 3-trifloyloxy-1*H*-pyrazole **3**. No formation of an unwanted mixture of *N*- and *O*-triflated products was found, in contrast to an observation reported earlier regarding the low regioselectivity of a similar triflation of 1-substituted pyrazol-5-ones.[14c]

The selective monobromination at C-4 of **2** was performed with 1 equiv of Br_2 in chloroform at room temperature, similarly to a previously described procedure,[20] yielding 4-bromo-1-phenyl-1*H*-pyrazol-3-ol (**4**). There are several methods known for the preparation of 4-iodo-1*H*-pyrazoles, including green iodination with iodine/hydrogen peroxide in water.[21] However, due to the low solubility of compound **2** in such a solvent, we have instead used a procedure described by Roy et al. for the iodination of indole at the C-3 position.[22] When compound **2** was treated with iodine and potassium hydroxide in DMF, 4-iodo-1-phenyl-1*H*-pyrazol-3-ol (**6**) was formed in good yield (Scheme 1). The dibrominated pyrazole **7** was obtained by refluxing compound **2** with 3 equiv of Br_2 in $CHCl_3$ (simultaneously introducing a bromo atom into both the phenyl and the pyrazole moieties) as we have described previously.[23] Treatment of 4-bromopyrazole **4** and 4,4′-dibromopyrazole **7** with triflic anhydride in the presence of triethylamine afforded multiply halogenated and pseudohalogenated substrates **5** and **8**, respectively.



Scheme 1. Reagents and conditions: (i) $FeCl_3$, HCl (aq), EtOH, reflux, 1 h or $FeCl_3$, DMF, 80 °C, 4 days; (ii) Tf_2O, TEA, DCM, rt, 2 h (for **3**, **5**, and **8**); (iii) 1 equiv Br_2, $CHCl_3$, rt, 20 h; (iv): I_2, KOH, DMF, rt, 20 h; (v) 3 equiv Br_2, CCl_4, reflux, 19 h.

The use of *O*-triflated variants in cross-coupling strategies represents an efficient approach for installing various heterocycles into complex molecules.[24] Having successfully prepared 3-trifloyloxy-1*H*-pyrazole **3**, we examined its ability to participate in Heck, Sonogashira and Suzuki cross-coupling reactions (Scheme 2).



Scheme 2. Reagents and conditions: (i) $H_2C{=}CHCO_2$-*t*-Bu, $Pd(PPh_3)_2Cl_2$, TEA, DMF, 120 °C, 16 h (for **9a**); (ii) CH≡CPh, $Pd(PPh_3)_2Cl_2$, CuI, TEA, DMF, 55 °C, 5 days (for **9b**); (iii) arylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, KBr, dioxane, reflux, 6–17 h (for **9c**–**e**).

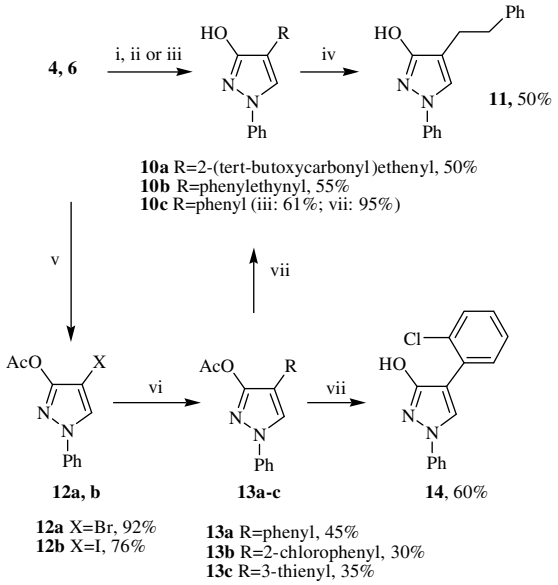
Under the Heck reaction conditions,[25] 3-trifloylpyrazole **3** was successfully coupled with *tert*-butyl acrylate using $Pd(PPh_3)_2Cl_2$ as a catalyst in DMF containing TEA to give product **9a** at a 74% yield. The standard Sonogashira reaction conditions[26] ($Pd(PPh_3)_2Cl_2$, CuI, triethylamine) were applied to obtain the cross-coupling product **9b** (55%) from triflate **3** and phenylacetylene. The Suzuki reaction[27] was used for the cross-coupling of triflate **3** with various boronic acids (phenyl-, 2-thiophene-, 3-thiophene-) to give **9c**–**e**, respectively, in good yields. In this case, $Pd(PPh_3)_4$ was used as a catalyst, and the reaction was carried out in the presence of KBr, which prevents the decomposition of the catalyst as reported elsewhere.[14c,27b] The Suzuki reaction of compound **3** was also examined with 2-furylboronic acid under the conditions described above. However, this coupling did not give a positive result as a complex reaction mixture was obtained (Scheme 3) with full consumption of the starting compound **3**.

Further, we investigated the cross-coupling reactions of the halogenated compounds **4** and **6**, which possess the hydroxyl functionality at the C-3 position. The presence of electron-donating groups on the aromatic ring of arylhalides is known to often decrease the rate of the cross-coupling reaction rate.[27b] More specifically, the reactivity of phenol halides can also be substantially lowered if the hydroxylate donor group forms under the influence of base.[28] However, formation of unwanted phenolates can be avoided by protecting the hydroxyl groups, for example, by their transformation to the corresponding ethers or esters.[29]

Thus, 4-bromopyrazol-3-ol (**4**) was coupled with *tert*-butyl acrylate under Heck reaction conditions to afford product **10a** at a moderate yield of 50%. Employing 4-iodopyrazol-3-ol **6** as the starting material under analogous reaction conditions, only a 20% yield of **10a** was obtained.

Both 4-halopyrazol-3-ols **4** and **6** were also tested under Sonogashira reaction conditions using the $Pd(PPh_3)_2Cl_2$/CuI catalytic system in DMF. However, in this case only the iodinated pyrazole **6** gave the desired product **10b**, which was subsequently hydrogenated to give **11** (Scheme 3). The Sonogashira coupling was also examined with but-3-yn-1-ol, but no target product was formed under the above-mentioned conditions. Under Stille coupling

conditions[30] ($Pd(PPh_3)_2Cl_2$ as a catalyst in DMF), 4-bromopyrazol-3-ol **4** was successfully coupled with phenyltributyltin to give **10c** (Scheme 3).



Scheme 3. Reagents and conditions: (i) $H_2C{=}CHCO_2$-*t*-Bu, $Pd(PPh_3)_2Cl_2$, TEA, DMF, 120 °C, 5 h (for **10a**); (ii) CH≡CPh, $Pd(PPh_3)_2Cl_2$, CuI, TEA, DMF, 55 °C, 8 h (for **10b**); (iii) $SnBu_3Ph$, $Pd(PPh_3)_2Cl_2$, DMF, 80 °C, 12 h (for **10c**); (iv) H_2, Pd/C, rt, 50 bar, 1 day; (v) Ac_2O, reflux, 30 min; (vi) arylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, KBr, dioxane, reflux, 3–6 h; (vii) 1 N NaOH, MeOH, 60 °C, 2 h.

However, the efforts to perform Suzuki couplings with the 4-halopyrazoles **4** and **6** and phenylboronic acid using $Pd(PPh_3)_4$ as a catalyst and employing various conditions reported in the literature[31] (Na_2CO_3 in DME/H_2O; NaOH in toluene/H_2O; K_3PO_4 in toluene/H_2O; Bu_4NF in toluene; K_3PO_4 in toluene) failed, and only dehalogenated pyrazole was obtained. Thus, we next examined whether the protection of the hydroxyl group could influence the outcome of the Suzuki reaction. It was recently reported that 4-halo-1-phenyl-1*H*-pyrazoles with the 3-hydroxyl moiety protected by alkylation easily underwent Suzuki cross-coupling with arylboronic acids.[14e] However, the conditions used in that work for the subsequent cleavage of the 3-alkoxy group and liberation of the hydroxyl functionality were rather harsh, and in principle not compatible with many functional groups. In our case, 'blocking' of the hydroxyl functionality was achieved by treatment of pyrazol-3-ols **4** and **6** with boiling acetic anhydride,[32] allowing us to obtain the esters **12a** and **12b**, respectively (Scheme 3).

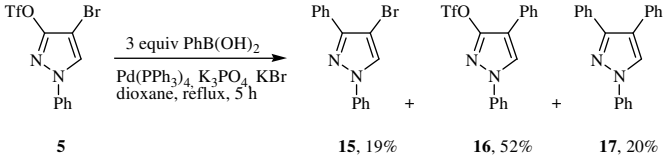
Having in hand the 'protected' scaffolds **12a** and **12b**, a brief study of the Suzuki reaction with phenylboronic acid was undertaken (Table 1), indicating a preference for bromopyrazole **12a** as a substrate in the cross-coupling protocol (Scheme 3).

Table 1
Conditions for the Suzuki reactions of **12a**, **b** with phenylboronic acid using $Pd(PPh_3)_4$ as a catalyst

Starting compound	Base and solvent (reflux)	Time, h	Yield, %
12b	Na_2CO_3, DME/H_2O	22	—
12b	K_3PO_4, Toluene	20	8
12a	K_3PO_4, Toluene	16	40
12a	K_3PO_4, KBr, 1,4-dioxane	5	60

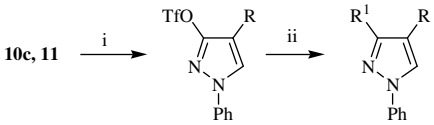
After optimizing the reaction conditions, we performed Suzuki couplings with other boronic acids: 2-chlorophenyl- and 3-thiopheneboronic acids to obtain the desired functionalized pyrazoles **13b** and **13c** (Scheme 3). In the next step, the acetyl groups of **13a** and **13b** were easily removed under standard conditions (1 N NaOH in MeOH) to give pyrazol-3-ols **10c** and **14**.

Pd-catalyzed cross-coupling reactions of multiply halogenated heterocycles are widely used in the construction of highly functionalized organic compounds.[33] It is known that the main factors determining regioselectivity in cross-coupling reactions of heterocycles multiply substituted by identical halogen atoms include various electronic and steric effects and the coordinating features of ring heteroatoms.[33] When the halogen atoms are different, the regioselectivity is mainly due to the bond dissociation energies of the respective carbon–halogen bonds.[34] Therefore, the bromine atom might be expected to undergo substitution more readily than the TfO group, as the relative bond dissociation energy of the C–Br bond is lower than that of the C–O bond.[35] In our case, this expectation was corroborated by the cross-coupling reaction of 4-bromo-3-trifloyloxy-1*H*-pyrazole (**5**). Treatment of the latter with phenylboronic acid under Suzuki reaction conditions afforded a mixture of products **15**, **16**, and **17**, indicating that substitution at the 4-position of the pyrazole nucleus is preferred (Scheme 4). In order to achieve full consumption of the starting compound **5**, we used a threefold excess of phenylboronic acid. In this case, the ratio of products **15**, **16**, and **17** (established by both ^1H NMR analysis of the crude mixture and the relative yields of purified products) was 1:2.7:1. When using 4 equiv of phenylboronic acid and refluxing the reaction mixture for 20 h, only 1,3,4-triphenyl-1*H*-pyrazole **17** was obtained, in a 70% yield. Synthesis of the latter has previously been described in the literature.[36]



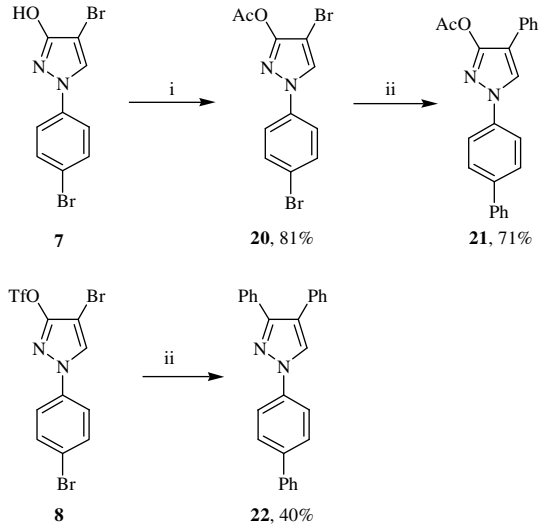
Scheme 4. Reagents and conditions: (i) phenylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, KBr, dioxane, reflux, 6 h.

A regiospecific construction of different 3,4-disubstituted 1-phenyl-1*H*-pyrazoles could be achieved by employing the successfully prepared adducts **10** and **11** as the intermediates for a second cross-coupling reaction. Thus, transformation of the pyrazol-3-ols **10c** and **11** into the triflates **16** and **18**, respectively, yielded effective electrophiles that easily participated in Suzuki cross-coupling with phenylboronic acid to afford the trisubstituted pyrazoles **19a** and **19b**, respectively (Scheme 5).



Scheme 5. Reagents and conditions: (i) Tf_2O, TEA, DCM, rt, 2 h; (ii) arylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, KBr, dioxane, reflux, 4 h.

Recently, an efficient protocol for the arylation of 1-phenylpyrazole in 2-position of the phenyl ring has been published.[37] We performed a related coupling by reacting 3-acyloxy-4,4′-dibromopyrazole **20** with phenylboronic acid (3 equiv) using $Pd(PPh_3)_4$ as the catalyst (Scheme 6). The reaction afforded product **21** in good yield, in which both bromo atoms of reactant **20** were replaced by phenyl rings. Furthermore, treatment of the dibrominated 3-trifloyloxy pyrazole **8** with 6 equiv of phenylboronic acid for 24 h under the same reaction conditions afforded the trisubstitution product **22** in a 40% yield (Scheme 6).



Scheme 6. Reagents and conditions: (i) Ac_2O, reflux, 30 min; (ii) phenylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, KBr, dioxane, reflux, 5–24 h.

3. Conclusions

In conclusion, we have developed a general approach for the preparation of (het)aryl- and carbo-functionally substituted 1-phenyl-1*H*-pyrazoles via Pd(0)-catalyzed cross-coupling reactions starting from 1-phenylpyrazol-3-ol.[38]

4. Experimental

4.1. General

Melting points were determined on a Reichert–Kofler hot-stage microscope or Melt-Temp (Capillary Melting point Apparatus) and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV), on a Waters ZQ 2000 (APCI+, 20 V) instrument and on a Finnigan MAT 8230 instrument (EI, 70 eV, HRMS). IR spectra were recorded on a Perkin–Elmer FTIR 1605 spectrophotometer or on a Perkin–Elmer FTIR spectrum 1000 spectrometer. Elemental analyses (C, H, and N) were performed at the Microanalytical Laboratory, University of Vienna, and were in good agreement (±0.4%) with the calculated values. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C). The center of the signal was used as an internal standard, which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$), δ 2.49 ppm (^{1}H in DMSO-d_6), δ 77.0 ppm (^{13}C in $CDCl_3$), and δ 39.5 ppm (^{13}C in DMSO-d_6). ^{15}N NMR spectra were obtained on a Bruker Avance 500 instrument with a 'directly' detecting broadband observation probe, and were referenced against external nitromethane. Digital resolutions were 0.25 Hz/data point in the ^{1}H spectra and 0.4 Hz/data point in the ^{13}C NMR spectra.

4.2. Synthetic procedures

*4.2.1. General procedure for pyrazole triflation (compounds **3**, **5**, **8**, **16**, and **18**)*

The appropriate pyrazole (**2**, **4**, **10c** or **11**) (3 mmol), trifluormethanesulfonic anhydride (889 mg, 3.15 mmol), and triethylamine (0.5 mL, 3.6 mmol) were dissolved in dichloromethane (10 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water (15 mL) and extracted with ethyl acetate (3×20 mL). Organic layers were combined, washed with brine, and dried over sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, eluent ethyl acetate/hexane, 1:4 v/v).

*4.2.1.1. 1-Phenyl-1H-pyrazol-3-yl trifluoromethane sulfonate **3**.* Yield 690 mg, 79%; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.35 (d, ^3J=2.6 Hz, 1H, H-4), 7.34 (m, 1H, Ph H-4), 7.47 (m, 2H, Ph H-3,5), 7.63 (m, 2H, Ph H-2,6), 7.87 (d, ^3J=2.6 Hz, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.5 (C-4, ^1J=185.2 Hz, ^2J(C4,H5)=8.1 Hz, ^5J(C4,CF_3)=0.6 Hz), 118.7 (CF_3, ^1J=321.1 Hz), 119.1 (Ph C-2,6), 127.4 (Ph C-4), 128.7 (C-5, ^1J=190.7 Hz, ^2J(C5,H4)=7.8 Hz), 129.6 (Ph C-3,5), 139.2 (Ph C-1), 153.7 (C-3, ^2J(C3,H4)=1.1 Hz, ^3J(C3,H5)=11.9 Hz); ^{15}N NMR (50 MHz, $CDCl_3$): δ −174.3 (N-1), −98.9 (N-2); IR (KBr): 3158 (CH_{arom}), 1601, 1531, 1448, 1430, 1250, 1224, 1056, 1011 cm^{-1}; MS *m*/*z* (%): 292 (M^+, 34), 159 ($[M-CF_3SO_2]^+$, 100), 77 ($C_6H_5^+$, 95). Anal. Calcd for $C_{10}H_7F_3N_2O_3S$: C, 41.10; H, 2.41; N, 9.59. Found: C, 41.37; H, 2.40; N, 9.64.

*4.2.1.2. 4-Bromo-1-phenyl-1H-pyrazol-3-yl trifluoro methanesulfonate **5**.* Yield 864 mg, 78%; white solid; mp 36–37 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (m, 1H, Ph H-4), 7.48 (m, 2H, Ph H-3,5), 7.59 (m, 2H, Ph H-2,6), 7.92 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 87.2 (C-4, ^2J(C4,H5)=5.3 Hz), 118.6 (CF_3, ^1J=321.3 Hz), 118.9 (Ph C-2,6), 127.9 (Ph C-4), 129.1 (C-5, ^1J=195.9 Hz), 129.7 (Ph C-3,5), 138.8 (Ph C-1), 151.6 (C-3, ^3J(C3,H5)=10.3 Hz); ^{15}N NMR (50 MHz, $CDCl_3$): δ −174.5 (N-1), N-2 was not found; IR (KBr): 3151 (CH_{arom}), 1451, 1422, 1244, 1232, 1137, 1073, 757, 729, 608, 514 cm^{-1}; MS *m*/*z* (%): 372/370 (M^+, 9), 239/237 ($[M-CF_3SO_2]^+$, 39), 77 ($C_6H_5^+$, 100). Anal. Calcd for $C_{10}H_5Br_2F_3N_2O_3S$: C, 32.36; H, 1.62; N, 7.55. Found: C, 32.70; H, 1.60; N, 7.30.

*4.2.1.3. 4-Bromo-1-(4-bromophenyl)-1H-pyrazol-3-yl trifluoro methanesulfonate **8**.* Yield 1.07 g, 79%; white solid; mp 55–56 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (m, 2H, Ph-3,5), 7.60 (m, 2H, Ph H-2,6), 7.90 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 87.8 (C-4), 118.6 (CF_3, ^1J=321.2 Hz), 120.3 (Ph C-2,6), 121.4 (Ph C-4), 129.0 (C-5), 132.8 (Ph C-3,5), 137.8 (Ph C-1), 151.8 (C-3); IR (KBr): 3101 (CH_{arom}), 1494, 1451, 1428, 1238, 1135, 1080, 1060, 834, 605, 656 cm^{-1}; MS *m*/*z* (%): 452/450/448 (M^+, 19/37/18), 319/317/315 ($[M-CF_3SO_2]^+$, 57/100/51), 157/155 ($[C_6H_4Br]^+$, 72/68). Anal. Calcd for $C_{10}H_5Br_2F_3N_2O_3S$: C, 26.69; H, 1.12; N, 6.22. Found: C, 27.08; H, 1.11; N, 5.83.

*4.2.1.4. 1,4-Diphenyl-1H-pyrazol-3-yl trifluoromethane sulfonate **16**.* Yield 994 mg, 90%; white solid; mp 58–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.70 (m, 10H, Ph), 8.06 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.8 (NPh C-2,6), 119.9 (CF_3, ^1J=321.4 Hz), 125.9, 127.0, 127.4, 127.9, 128.4, 128.6, 129.0, 129.6, 139.0, 139.6, 142.3; IR (KBr): 3121 (CH_{arom}), 1599, 1506, 1426, 1222, 1133, 767, 753 cm^{-1}; MS *m*/*z* (%): 369 ($[M+H]^+$, 5), 301 (25), 242 (100). Anal. Calcd for $C_{16}H_{11}F_3N_2O_3S$: C, 52.17; H, 3.01; N, 7.61. Found: C, 51.97; H, 3.16; N, 7.22.

*4.2.1.5. 1-Phenyl-4-(2-phenylethyl)-1H-pyrazol-3-yl trifluoromethane sulfonate **18**.* Yield 741 mg, 78%, colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (m, 2H, C*H*$_2$–CH_2–Ph), 2.95 (m, 2H, C*H*$_2$–Ph), 7.20–7.35 (m, 6H, Ar–H), 7.41–7.57 (m, 5H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9 (*C*H$_2$–CH_2–Ph), 35.6 (*C*H$_2$–Ph), 113 (C-4), 118.6 (CF_3, ^1J=321.2 Hz), 118.6 (NPh C-2,6), 126.3, 127.0, 128.5 (CPh C-2,3,5,6), 129.5 (NPh C-3,5), 139.2 (NPh C-1), 140.6 (CPh C-1), 152.1 (C-3); IR (KBr): 3065, 3030 (CH_{arom}), 2930, 2862 (CH_{aliph}), 1601, 1504, 1427, 1217, 1136, 756, 700 cm^{-1}; MS *m*/*z* (%): 397 ($[M+H]^+$, 100), 264 ($[M-CF_3SO_2+H]^+$, 85). Anal. Calcd for C, 54.54; H, 3.81; N, 7.07. Found: C, 54.76; H, 3.80; N, 6.95.

4.2.2. Iodination reaction: synthesis of 4-iodo-1-phenyl-1H-pyrazol-3-ol ***6***

A solution of **2** (992 mg, 6.2 mmol), iodine (2.39 g, 9.4 mmol), and KOH (0.9 g, 16 mmol) in dimethylformamide (10 mL) was stirred at room temperature for 20 h. Then, the mixture was poured into a sodium thiosulfate solution (1.0 g in 7 mL of water) and extracted with diethyl ether (3×20 mL). Organic layers were combined and dried over sodium sulfate, and the solvent was evaporated. The residue was recrystallized from 50% aqueous ethanol to give pure **6**. Yield 1.12 g, 63%; yellowish crystals; mp 169–171 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.18 (m, J=7.5 Hz, 1H, Ph H-4), 7.41 (m, 2H, Ph H-3,5), 7.67 (m, 2H, Ph H-2,6), 8.40 (s, 1H, H-5), 10.89 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 49.0 (C-4, ^2J(C4,H5)=6.3 Hz), 116.8 (Ph C-2,6), 125.2 (Ph C-4), 129.4 (Ph C-3,5), 132.5 (C-5, ^1J=193.8 Hz), 139.3 (Ph C-1), 162.7 (C-3, ^3J(C3,H5)=9.4 Hz); ^{15}N NMR (50 MHz, DMSO-d_6): δ −181.9 (N-1), −118.1 (N-2); IR (KBr): 3047 (OH) cm^{-1}; MS m/z (%): 287 ([M+1]$^+$, 11), 286 ([M$^+$, 100), 77 ($C_6H_5^+$, 87). Anal. Calcd for $C_9H_7IN_2O$: C, 37.79; H, 2.47; N, 9.79. Found: C, 37.94; H, 2.57; N, 9.72.

4.2.3. General procedure for the Heck reaction (compounds ***9a*** *and* ***10a****)*

Triethylamine (0.21 mL, 1.5 mmol), CH_2CHCOO-t-Bu (0.3 mL, 2 mmol), and Pd(PPh$_3$)$_2$Cl$_2$ (70 mg, 0.1 mmol) were added to a solution of the appropriate pyrazole (**3** or **4**) (1 mmol) in dry dimethylformamide (4 mL) under argon atmosphere. Then, the reaction mixture was stirred at 120 °C under an argon atmosphere for the given time. After cooling, the mixture was filtered over Celite, 10 mL of water was added, and extraction was done with dichloromethane (3×20 mL). Organic layers were combined, washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluent ethyl acetate/hexane, 1:6 v/v).

4.2.3.1. tert-Butyl (2E)-3-(1-phenyl-1H-pyrazol-3-yl)acrylate ***9a****.* The reaction mixture was stirred for 16 h. Yield 180 mg, 74%; colorless substance; mp 125–130 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.54 (s, 9H, CH_3), 6.42 (d, $^3J_{trans}$=16.1 Hz, 1H, COC*H*=CH), 6.67 (d, ^3J(H4,H5)=2.5 Hz, 1H, H-4), 7.30 (m, 1H, Ph H-4), 7.46 (m, 2H, Ph H-3,5), 7.66 (d, $^3J_{trans}$=16.1 Hz, 1H, COCH=C*H*), 7.69 (m, 2H, Ph H-2,6), 7.89 (d, ^3J(H5,H4)=2.5 Hz, 1H, H-5); ^{13}C NMR (75 MHz, CDCl$_3$): δ 28.2 (CH_3, ^1J=126.8 Hz, ^3J(CH_3,C*H*$_3$)=4.0 Hz, 80.4 (*C*(CH$_3$)$_3$), ^2J(C,CH$_3$)=4.0 Hz), 106.6 (C-4, ^1J=177.2 Hz, ^2J(C4,H5)=8.1 Hz, ^3J(C4, =CH)=4.3 Hz), 119.2 (Ph C-2,6), 122.2 (*C*OCH, ^1J=162.3 Hz, ^2J=3.4 Hz, 126.9 (Ph C-4), 128.1 (C-5, ^1J=188.0 Hz, ^2J(C5,H4)=8.9 Hz), 129.5 (Ph C-3,5), 135.2 (COCH=*C*H, ^1J=159.3 Hz), 139.8 (Ph C-1), 149.8 (C-3, ^2J(C3, =CH)=1.2 Hz, ^2J(C3,H4)=4.9 Hz, ^3J(C3,H5)=8.7 Hz, ^3J(C3,COCH) =6.3 Hz), 166.0 (C=O, ^2J(CO,COC*H*)=2.7 Hz, ^3J(CO, =CH)=6.7 Hz); ^{15}N NMR (50 MHz, CDCl$_3$): δ −161.0 (N-1), −77.0 (N-2); IR (KBr): 3137 (CH_{arom}), 2980 (CH_{aliph}), 1699, 1638, 1517, 1311, 1254, 1152 (C–O), 773, 755 cm^{-1}; ms: m/z 293 ([M+Na]$^+$, 30), 271 ([M+H]$^+$, 3). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.21; H, 6.68; N, 10.09.

4.2.3.2. tert-Butyl (2E)-3-(3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acrylate ***10a****.* The reaction mixture was stirred for 5 h. Yield 143 mg, 50%; yellow crystals; mp 189–190 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.31 (s, 9H, Me), 4.27 (br, 1H, OH), 6.20 (d, J_{trans}=15.8 Hz, 1H, COC*H*=CH), 7.04 (m, 1H, Ph H-4), 7.21 (m, 1H, Ph H-3,5), 7.27 (d, J_{trans}=15.8 Hz, 1H, COCH=*C*H), 7.36 (m, 2H, Ph H-2,6), 7.76 (s, 1H, H-5); ^{13}C NMR (75 MHz, CDCl$_3$): δ 27.6 (Me), 80.0 (*C*Me$_3$), 105.7 (C-4), 117.5 (Ph C-2,6), 125.7 (Ph C-4), 127.7, 128.9, 129.0, 132.9, 138.9, 161.4 (C-3), 167.7 (C=O); IR (KBr): 3101 (OH), 2974 (CH_{aliph}), 1698 (C=O), 1638, 1510, 1415, 1314 ,1215, 1151 (C–O), 751, 685 cm^{-1}; MS m/z (%): 309 ([M+Na]$^+$, 62). Anal. Calcd for $C_{16}H_{18}N_2O_3\cdot 2H_2O$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.61; H, 6.54; N, 8.84.

4.2.4. General procedure for the Sonogashira reaction (compounds ***9b*** *and* ***10b****)*

Triethylamine (0.42 mL, 3 mmol), phenylacetylene (0.32 mL, 3 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (140 mg, 0.2 mmol), and CuI (38 mg, 0.2 mmol) were added to a solution of the appropriate pyrazole (**3** or **6**) (2 mmol) in dry dimethylformamide (20 mL) under an argon atmosphere. The reaction mixture was stirred at 55 °C under an argon atmosphere for the given time. Then, the mixture was filtered over Celite, the solvent was evaporated, and the residue was purified by column chromatography.

4.2.4.1. 1-Phenyl-3-(phenylethynyl)-1H-pyrazole ***9b****.* The reaction mixture was stirred for 5 days and purified by column chromatography (SiO_2, eluent ethyl acetate/hexane, 1:20 v/v). Yield 244 mg, 50%; beige crystals; mp 130–135 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.67 (d, J=2.56 Hz, 1H, H-4), 7.29–7.74(m, 10H, Ph), (d, J=2.56 Hz, 1H, H-5); ^{13}C NMR (75 MHz, CDCl$_3$): δ 82.0 (C≡*C*Ph), 90.6 (*C*≡CPh), 111.7 (C-4), 119.3 (N–Ph C-2,6), 126.9, 127.3, 128.3, 128.6, 129.4, 131.7, 136.6 (N–Ph C-1), 139.7 (C-3); IR (KBr): 3147 (CH_{arom}), 1598, 1517, 1343, 756, 691 cm^{-1}; MS m/z (%): 246 ([M+2]$^+$, 10), 245 ([M+H]$^+$, 100). Anal. Calcd for $C_{17}H_{12}N_2\cdot 0.2H_2O$: C, 82.37; H, 5.04; N, 11.30. Found: C, 82.61; H, 5.21; N, 10.97.

4.2.4.2. 1-Phenyl-4-(phenylethynyl)-1H-pyrazol-3-ol ***10b****.* The reaction mixture was stirred for 8 h and purified by column chromatography (SiO_2, eluent dichloromethane/methanol, 100:1 v/v). Yield 286 mg, 55%; beige solid; mp 145–146 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.23 (m, 1H, NPh H-4), 7.38 (m, 1H, CPh H-4), 7.40 (m, 2H, CPh H-3,5), 7.45 (m, 2H, NPh H-3,5), 7.47 (m, 2H, CPh H-2,6), 7.72 (m, 2H, NPh H-2,6), 8.64 (s, 1H, H-5), 11.01 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 80.4 (PhC≡*C*, ^3J(C,H5)=1.7 Hz), 91.3 (C-4, ^2J(C4,H5)=6.8 Hz), 91.6 (Ph*C*≡C), 117.2 (NPh C-2,6), 122.9 (CPh C-1), 125.4 (NPh C-4), 128.2 (CPh C-4), 128.7 (CPh C-3,5), 129.4 (NPh C-3,5), 130.7 (C-5, ^1J=192.6 Hz), 130.9 (CPh C-2,6), 139.1 (NPh C-1), 162.7 (C-3, ^3J(C3,H5)=9.1 Hz); ^{15}N NMR (50 MHz, DMSO-d_6): δ −186.9 (N-1), −120.3 (N-2); IR (KBr): 3129 (OH), 1535, 1503, 1212, 1063, 761, 692 cm^{-1}; MS m/z (%): 283 ([M+Na]$^+$, 100), 261 ([M+H]$^+$, 5). Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 75.40; H, 4.80; N, 10.69.

4.2.5. Stille coupling: synthesis of 1,4-diphenyl-1H-pyrazol-3-ol ***10c***

Under inert and anhydrous conditions, **6** (100 mg, 0.42 mmol) was dissolved in dimethylformamide (5 mL). Pd(PPh$_3$)$_2$Cl$_2$ (14 mg, 0.02 mmol) and phenyltributyltin (0.16 mL, 0.5 mmol) were added to the solution, which was stirred at 80 °C for 12 h. DMF was removed under reduced pressure, the mixture was diluted with dichloromethane (50 mL), washed with potassium fluoride (aq) (30 mL), and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, eluent dichloromethane). Yield 60 mg, 61%; white solid; mp 189–196 °C (lit. mp 202–204 °C);[39] ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.25 (m, 1H, Ph H-4), 7.30 (m, 1H, NPh H-4), 7.41 (m, 2H, Ph H-3,5), 7.50 (m, 2H, NPh H-3,5), 7.61 (m, 2H, NPh H-2,6), 7.78 (m, 2H, Ph H-2,6), 7.99 (s, 1H, H-5), 12.00 (br, 1H, OH); ^{13}C NMR (75 MHz, CDCl$_3$): δ 109.3 (C-4), 118.6 (NPh C-2,6), 125.7 (C-5, ^1J=185.5 Hz), 126.0 (Ph C-2,6), 126.3 (NPh C-4), 126.5 (Ph C-4), 128.7 (Ph C-3,5), 129.7 (NPh C-3,5), 131.3 (Ph C-1), 139.3 (NPh C-1), 161.1 (C-3, ^3J(C3,5-H)=9.6 Hz); IR (KBr): 2961 (OH), 1600, 1536, 1505, 1250, 1215, 753, 692 cm^{-1}; MS m/z (%): 236 (M$^+$, 100), 77 ($C_6H_5^+$, 92). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.21; H, 5.22; N, 11.79.

4.2.6. General procedure for the Suzuki cross-coupling reaction (compounds ***9c–e***, ***13a–c***, ***15–17***, ***19a***, ***b***, ***21***, *and* ***22****)*

Anhydrous K_3PO_4 (636 mg, 3 mmol), an appropriate arylboronic acid, Pd(PPh$_3$)$_4$ (92 mg, 0.08 mmol), and KBr (131 mg, 1.1 mmol)

were added to a solution of the pyrazole (**3**, **5**, **8**, **12a**, **16**, **18** or **20**) (1 mmol) in 1,4-dioxane (10 mL) under an argon atmosphere. After refluxing under an argon atmosphere for the appropriate reaction time, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography.

*4.2.6.1. 1,3-Diphenyl-1H-pyrazole **9c**.* The coupling was performed with phenylboronic acid (366 mg, 3 mmol). The mixture was refluxed for 6 h and purified by column chromatography (SiO_2, eluent ethyl acetate/petrol ether, 1:8 v/v). Yield 143 mg, 65%; white solid; mp 81–83 °C (lit. mp 82–84 °C);[40] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.05 (s, 1H, 4-H), 7.32–7.94 (m, 10H, Ph), 8.58 (s, 1H, H-5); IR (KBr): 3136, 1600, 1527, 1506, 1455, 756, 686 cm^{-1}; MS *m*/*z* (%): 221 ([M+H]$^+$, 16), 220 (M$^+$, 100), 219 ([M–H]$^+$, 68), 77 ($C_6H_5^+$, 34). Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.80; H, 5.49; N, 12.71.

*4.2.6.2. 1-Phenyl-3-(thiophen-3-yl)-1H-pyrazole **9d**.* The coupling was performed with thiophene-3-boronic acid (384 mg, 3 mmol), a reaction time of 17 h and purification by column chromatography (SiO_2, eluent ethyl acetate/petrol ether, 1:8 v/v). Yield 136 mg, 60%; yellowish solid; mp 83–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66 (d, *J*=2.5 Hz, 1H, H-4), 7.29 (m, 1H, Ph H-4), 7.38 (dd, ^3J(H5,H4)=5.0 Hz, ^4J(H5,H2)=3.0 Hz, 1H, Th H-5), 7.47 (m, 2H, Ph H-3,5), 7.59 (dd, ^3J(H4,H5)=5.0 Hz, ^4J(H4,H2)=1.3 Hz, 1H, Th H-4), 7.68 (dd, ^4J(H2,H4)=1.3 Hz, ^4J(H2,H5)=3.0 Hz, 1H, Th H-2), 7.76 (m, 2H, Ph H-2,6), 7.92 (d, ^3J(H5,H4)=2.5 Hz, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$): δ 105.4 (C-4, ^1J=176.3 Hz, ^2J(C4,H5)=8.3 Hz), 119.0 (Ph C-2,6), 121.0 (Th C-2), 125.9 (Th C-5), 126.1 (Th C-4), 126.3 (Ph C-4), 127.7 (C-5, ^1J=186.9 Hz, ^2J(C5,H4)=9.0 Hz), 129.4 (Ph C-3,5), 135.0 (Th C-3), 140.2 (Ph C-1), 149.3 (C-3); ^{15}N NMR (50 MHz, $CDCl_3$): δ −166.6 (N-1), N-2 was not found; IR (KBr): 3092 (CH_{arom}), 1599, 1497, 788, 754 cm^{-1}; MS *m*/*z* (%): 227 ([M+H]$^+$, 18), 226 (M$^+$, 100), 225 ([M−H]$^+$, 51), 77 ($C_6H_5^+$, 23). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found: C, 68.84; H, 4.53; N, 11.95.

*4.2.6.3. 1-Phenyl-3-(thiophen-2-yl)-1H-pyrazole **9e**.* The coupling was performed with thiophene-2-boronic acid (384 mg, 3 mmol), a reaction time of 15 h and purification by column chromatography (SiO_2, eluent ethyl acetate/petrol ether, 1:8 v/v). Yield 120 mg, 53%; yellowish solid; mp 63–65 °C (lit. mp 52–53 °C);[40] ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68 (d, ^3J(H4,H5)=2.5 Hz, 1H, H-4), 7.09 (dd, ^3J(H4,H3)=3.6 Hz, ^3J(H4,H5)=5.1 Hz, 1H, Th H-4), 7.29 (m, 1H, Ph H-4), 7.29 (dd, ^3J(H5,H4)=5.1 Hz, ^4J(H5,H3)=1.2 Hz, 1H, Th H-5), 7.42 (dd, ^3J(H3,H4)=3.6 Hz, ^4J(H3,H5)=1.2 Hz, 1H, Th H-3), 7.46 (m, 2H, Ph H-3,5), 7.74 (m, 2H, Ph H.2,6), 7.92 (d, ^3J(H5,H4)=2.5 Hz, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$): δ 105.1 (C-4, ^1J=177.4 Hz, ^2J(C4,H5)=8.3 Hz), 119.0 (Ph C-2,6), 124.2 (Th C-3, ^1J=166.5 Hz, ^2J(C3,H4)=5.9 Hz, ^3J(C3,H5)=9.4 Hz), 124.9 (Th C-5, ^1J=185.9 Hz, ^2J(C5,H4)=6.8 Hz, ^3J(C5,H3)=10.6 Hz), 126.4 (Ph C-4), 127.4 (Th C-4, ^1J=167.8 Hz, ^2J(C4,H3)=5.4 Hz, ^2J(C4,H5)=3.7 Hz), 128.0 (C-5, ^1J=187.4 Hz, ^2J(C5,H4)=8.9 Hz), 129.4 (Ph C-3,5), 136.3 (Th C-2), 139.9 (Ph C-1), 148.2 (C-3); ^{15}N NMR (50 MHz, $CDCl_3$): δ −165.3 (N1), N-2 was not found; IR (KBr): 1598, 1507, 1374 (C=C, C–N), 760, 688 (CH=CH of monosubstituted benzene) cm^{-1}; MS *m*/*z* (%): 227 ([M+H]$^+$, 18), 226 (M$^+$, 100), 225 ([M−H]$^+$, 34), 77 ($C_6H_5^+$, 23). Anal. Calcd for $C_{13}H_{10}N_2S\cdot 0.4H_2O$: C, 66.87; H, 4.66; N, 12.00. Found: C, 67.19; H, 4.47; N, 11.60. HRMS Calcd for $C_{13}H_{10}N_2S$: 226.0565. Found: 226.0563.

*4.2.6.4. 1,4-Diphenyl-1H-pyrazol-3-yl acetate **13a**.* The coupling was performed with phenylboronic acid (366 mg, 3 mmol), a reaction time of 5 h and purification by column chromatography (SiO_2, eluent dichloromethane). Yield 167 mg, 60%; white solid; mp 94–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 7.30 (m, 1H, NPh H-4), 7.30 (m, 1H, CPh H-4), 7.40 (m, 2H, CPh H-3,5), 7.46 (m, 2H, NPh H-3,5), 7.49 (m, 2H, CPh H-2,6), 7.68 (m, 2H, NPh H-2,6), 8.05 (s, 1H, H-5); ^{13}C NMR (75 Hz, $CDCl_3$): δ 20.8 (CH_3, ^1J=130.4 Hz), 114.9 (C-4, ^2J(C4,H5)=7.1 Hz, ^3J(C4, Ph H-2,6)=4.1 Hz), 118.7 (NPh C-2,6), 125.6 (C-5, ^1J=187.5 Hz), 126.6 (CPh C-2,4,6), 127.1 (NPh C-4), 128.9 (CPh C-3,5), 129.4 (NPh C-3,5), 130.4 (CPh C-1), 139.6 (NPh C-1), 153.3 (C-3, ^3J(C3,H5)=9.9 Hz), 168.4 (CO, ^2J(CO,CH_3)=7.1 Hz); IR (KBr): 3113 (CH_{arom}), 1759 (C=O), 1594, 1509, 1408, 1211, 1180, 761, 754, 701, 691 cm^{-1}; MS *m*/*z* (%): 278 (M$^+$, 4), 236 (100), 77 ($C_6H_5^+$, 28). Anal. Calcd for $C_{17}H_{14}N_2O_2\cdot 0.4H_2O$: C, 71.51; H, 5.22; N, 9.81. Found: C, 71.39; H, 4.88; N, 9.76.

*4.2.6.5. 4-(2-Chlorophenyl)-1-phenyl-1H-pyrazol-3-yl acetate **13b**.* The coupling was performed with 2-chlorophenylboronic acid (469 mg, 3 mmol), a reaction time of 3 h and purification by column chromatography (SiO_2, eluent ethyl acetate/petrol ether, 1:8 v/v). Yield 92 mg, 30%; white crystals; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3), 7.71–7.28 (m, 9H, Ph), 8.14 (s, 1H, H-4); MS *m*/*z* (%): 314/312 (M$^+$, 0.2/0.6), 272/270 (6/21), 160 (61), 77 ($C_6H_5^+$, 72), 43 (CH_3CO^+, 100). The material was immediately converted into compound **14**.

*4.2.6.6. 1-Phenyl-4-(thiophen-3-yl)-1H-pyrazol-3-yl acetate **13c**.* The coupling was performed with thiophene-3-boronic acid (384 mg, 3 mmol), a reaction time of 6 h and purification by column chromatography (SiO_2, eluent ethyl acetate/hexane, 1:10 v/v). Yield 100 mg, 35%; white solid; mp 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H, CH_3), 6.66 (m, 1H, H-4), 7.24–7.50 (m, 5H, Ar–H), 7.69 (m, 2H, Ph H-2,6), 8.06 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8 (CH_3), 110.6 (C-4), 118.6, 120.2, 125.2, 126.2, 126.5, 129.4, 130.2, 139.4, 153.1, 168.4 (C=O); IR (KBr): 3107 (CH_{arom}), 1758 (C=O), 1594, 1518, 1209, 759, 692 cm^{-1}; MS *m*/*z* (%): 308 ([M+Na+H]$^+$, 10), 307 ([M+Na]$^+$, 46]), 285 ([M+H]$^+$, 10), 243 (100). Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.75; H, 4.49; N, 10.28.

*4.2.6.7. General procedure for the synthesis of **15**–**17**.* The coupling was performed with phenylboronic acid (366 mg, 3 mmol), a reaction time of 5 h and purification by column chromatography (SiO_2, eluent ethyl acetate/hexane, 1:10 v/v) to give **15**, **16**, and **17** in separate fractions.

*4.2.6.7.1. 4-Bromo-1,3-diphenyl-1H-pyrazole **15**.* Yield 56 mg, 19%; colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.50 (m, 6H, Ph), 7.73 (m, 2H, NPh H-2,6), 8.01 (m, 2H, CPh H-2,6), 8.03 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 94.4 (C-4), 118.8 (NPh C-2,6), 126.9, 127.8, 128.4, 128.5, 128.8, 129.5, 131.7, 139.8, 150.0 (C-3); IR (KBr): 3139, 3061 (CH_{aliph}), 1600, 1511, 754, 687 cm^{-1}; MS *m*/*z* (%): 300/298 (M$^+$, 22/24), 77 ($C_6H_5^+$, 100). Anal. Calcd for $C_{15}H_{11}BrN_2$: C, 60.22; H, 3.71; N, 9.36. Found: C, 59.65; H, 3.86; N, 8.86.

*4.2.6.7.2. 1,4-Diphenyl-1H-pyrazol-3-yl trifluoro methanesulfonate **16**.* Yield 191 mg, 52%.

*4.2.6.7.3. 1,3,4-Triphenyl-1H-pyrazole **17**.* Yield 60 mg, 20%, white solid; mp 90–91 °C (lit. mp 92–93 °C);[41] ^{1}H NMR ($CDCl_3$): δ 7.30–7.84 (m, 15H, Ph), 8.04 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 118.9 (N–Ph C-2,6), 122.9 (C-4), 126.4, 126.6, 126.9, 127.8, 128.3, 128.4, 128.5, 128.6, 129.4, 132.8, 133.1, 139.9 (N-Ph C-1), 150.4 (C-3); IR (KBr): 3047 (CH_{arom}), 1598, 1501, 767, 956, 698, 692 cm^{-1}; MS *m*/*z* (%): 298 ([M+2]$^+$, 25), 297 ([M+H]$^+$, 100). Anal. Calcd for $C_{21}H_{16}N_2\cdot 0.3H_2O$: C, 83.42; H, 5.56; N, 9.26. Found: C, 83.74; H, 5.49; N, 9.21.

*4.2.6.8. 1,4-Diphenyl-3-(thiophen-3-yl)-1H-pyrazole **19a**.* The coupling was performed with thiophene-3-boronic acid (384 mg, 3 mmol), a reaction time of 4 h and purification by column

chromatography (SiO_2, acetate/hexane, 1:20 v/v). Yield 254 mg, 84%; colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.51 (m, 11H, Ar–H), 7.79 (m, 2H, NPh H-2,6), 7.98 (s, 1H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.8 (NPh C-2,6), 119.0, 123.0, 125.1 (NPh C-4), 126.4, 126.5, 127.2, 127.5, 128.5, 129.0, 129.4 (NPh C-3,5), 132.8 (CPh C-1), 133.9 (Th C-1), 139.8 (NPh C-1), 146.4 (C-3); IR (KBr): 3107, 3052 (CH_{arom}), 1600, 1505, 1406, 1335, 792, 756, 724, 700, 690 cm^{-1}; MS *m*/*z* (%): 303 ([M+H]$^+$, 100). Anal. Calcd for C, 75.47; H, 4.67; N, 9.26. Found: C, 75.07; H, 4.67; N, 9.45.

4.2.6.9. 1,3-Diphenyl-4-(2-phenylethyl)-1H-pyrazole ***19b***. The coupling was performed with phenylboronic acid (366 mg, 3 mmol), a reaction time of 4 h and purification by column chromatography (SiO_2, eluent ethyl acetate/hexane, 1:20 v/v). Yield 285 mg, 88%; white crystals; mp 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 (m, 2H, C*H*$_2$–CH$_2$–Ph), 3.08 (m, 2H, C*H*$_2$–Ph), 7.24–7.53 (m, 12H, Ar–H), 7.75–7.81 (m, 4H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7 (*C*H$_2$–CH$_2$–Ph), 36.4 (*C*H$_2$–Ph), 118.7 (NPh C-2,6), 119.0, 118.7, 126.0, 126.1, 126.2, 127.7, 127.8, 128.4, 128.4, 128.5, 129.3, 133.7, 141.1, 141.5, 151.43 (C-3); IR (KBr): 3061, 3028 (CH_{arom}), 2948, 2924 (CH_{aliph}), 1600, 1505, 1402, 763, 747, 695 cm^{-1}; MS *m*/*z* (%): 325 ([M+H]$^+$, 100). Anal. Calcd for C, 85.15; H, 6.21; N, 8.63. Found: C, 84.82; H, 6.17; N, 8.85.

4.2.6.10. 1-(Biphenyl-4-yl)-4-phenyl-1H-pyrazol-3-yl acetate ***21***. The coupling was performed with phenylboronic acid (488 mg, 4 mmol), a reaction time of 5 h and purification by column chromatography (SiO_2, eluent ethyl acetate/hexane, 1:10 v/v). Yield 250 mg, 71%; white solid; mp 101–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (CH_3), 7.16–7.64 (m, 14H, Ph), 8.04 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3 (CH_3), 118.7 (NPh C-2,6), 125.7, 126.2, 126.6, 127.0, 127.3, 127.7, 127.78, 128.6, 130.0, 138.3, 139.3, 139.4, 153.0, 168.6 (C=O); IR (KBr): 3036 (CH_{arom}), 1768 (C=O), 1373, 1203, 1183, 833, 763, 693 cm^{-1}; MS *m*/*z* (%): 377 ([M+Na]$^+$, 15), 340 (25), 339 ([M−CH_3]$^+$, 100). Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 77.69; H, 5.26; N, 8.00.

4.2.6.11. 1-(Biphenyl-4-yl)-3,4-diphenyl-1H-pyrazole ***22***. The coupling was performed with phenylboronic acid (732 mg, 6 mmol), a reaction time of 24 h and purification by column chromatography (SiO_2, eluent ethyl acetate/hexane, 1:10 v/v). Yield 150 mg, 40%; yellowish solid; mp 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.90 (m, 19H, Ph), 8.06 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 119.1 (NPh C-2,6), 123.0, 125.1, 126.5, 126.9, 127.4, 127.9, 128.0, 128.3, 128.4, 128.5, 128.7, 128.8, 132.8, 139.0, 139.2, 140.1 (C-3); IR (KBr): 3052 (CH_{arom}), 1527, 1493, 841, 762, 698 cm^{-1}; MS *m*/*z* (%): 374 ([M+H]$^+$, 33), 373 (M$^+$, 100). Anal. Calcd for $C_{23}H_{18}N_2O_2\cdot 0.2H_2O$: C, 86.23; H, 5.47; N, 7.45. Found: C, 85.88; H, 5.59; N, 7.47.

4.2.7. General procedure for the deacetylation (compounds ***10c*** *and* ***14****)*

A solution of the appropriate pyrazole (1 mmol), 1 N NaOH (6 mL), and methanol (5 mL) was stirred at 60 °C for 1 h. The reaction mixture was neutralized with 2 N HCl (to pH 7), cooled in the refrigerator and the precipitated product was collected by filtration, washed with water, and dried.

4.2.7.1. 1,4-Diphenyl-1H-pyrazol-3-ol ***10c***. Yield 224 mg, 95%.

4.2.7.2. 4-(2-Chlorophenyl)-1-phenyl-1H-pyrazol-3-ol ***14***. Yield 120 mg, 60%; white crystals; mp 203–213 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.22 (m, 1H, NPh H-4), 7.29 (m, 1H, CPh H-4), 7.36 (m, 1H, CPh H-5), 7.45 (m, 2H, NPh H-3,5), 7.52 (m, 1H, CPh H-3), 7.63 (m, 1H, CPh H-6), 7.75 (m, 2H, NPh H-2,6), 8.52 (s, 1H, H-5), 10.78 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 106.1 (C-4), 116.2 (NPh C-2,6), 125.0 (NPh C-4), 126.9 (CPh C-5), 127.7 (C-5, ^1J=190.1 Hz), 128.1 (CPh C-4), 129.4 (NPh C-3,5), 129.6 (CPh C-3), 130.2 (CPh C-1), 131.3 (CPh C-6), 131.7 (CPh C-2), 139.5 (NPh C-1), 160.0 (C-3, ^3J(C3,H5)=9.6 Hz); ^{15}N NMR (50 MHz, DMSO-d_6): δ −188.3 (N-1), −121.8 (N-2); IR (KBr): 3058 (OH), 1609, 1538, 1507, 1068, 1013, 742, 689 cm^{-1}; MS *m*/*z* (%): 272/270 (M$^+$, 33/100), 235 (50), 77 ($C_6H_5^+$, 31). Anal. Calcd for $C_{15}H_{11}ClN_2O\cdot 0.4H_2O$: C, 64.82; H, 4.28; N, 10.08. Found: C, 64.44; H, 4.02; N, 10.06.

4.2.8. 1-Phenyl-4-(2-phenylethyl)-1H-pyrazol-3-ol ***11***

Compound **10b** (260 mg, 1 mmol) was dissolved in absolute methanol (5 mL) and Pd/C (13 mg, 10%) was added under an argon atmosphere. The mixture was stirred for 1 day under a 50 bar hydrogen atmosphere at room temperature. The mixture was then filtered over Celite and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, eluent ethyl acetate/hexane, 1:3 v/v). Yield 211 mg, 80%; beige solid; mp 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (m, 2H, C*H*$_2$–CH$_2$–Ph), 2.96 (m, 2H, C*H*$_2$–Ph), 7.21 (m, 1H, NPh H-4), 7.23 (m, 1H, CPh H-4), 7.25 (m, 2H, CPh H-2,6), 7.28 (m, 2H, CPh H-3,5), 7.36 (s, 1H, H-5), 7.45 (m, 4H, NPh H-2,3,5,6), 11.70 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2 (*C*H$_2$–CH$_2$–Ph), 35.7 (*C*H$_2$–Ph), 108.1 (C-4), 118.0 (NPh C-2,6), 125.3 (NPh C-4), 125.9 (CPh C-4), 126.9 (C-5), 128.3 (CPh C-3,5), 128.6 (CPh C-2,6), 129.5 (NPh C-3,5), 139.6 (NPh C-1), 141.8 (CPh C-1), 162.3 (C-3); IR (KBr): 3136 (OH), 1561, 1506, 1320, 1252, 751, 688 cm^{-1}; MS *m*/*z* (%): 264 (M$^+$, 12), 173 ([M−Bn]$^+$, 100), 91 (16), 77 (21). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 76.87; H, 6.35; N, 11.00.

4.2.9. Acetylation: synthesis of 4-iodo-1-phenyl-1H-pyrazol-3-yl acetate ***12b***

Compound **6** (500 mg, 1.75 mmol) and an excess of acetic anhydride (6 mL) were heated to reflux for 30 min. Then, 10 mL of water were added and the solution was stirred for 30 min at rt. The mixture was poured into ice-water (30 mL), and after 30 min of stirring the precipitate was collected by filtration, washed with water, and dried. Yield 434 mg, 76%; white crystals; mp 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 7.30 (m, 1H, Ph H-4), 7.44 (m, 2H, Ph H-3,5), 7.59 (m, 2H, Ph H-2,6), 7.90 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5 (CH_3, ^1J=130.7 Hz), 52.6 (C-4, ^2J(C4,H5)=6.2 Hz), 118.7 (Ph C-2,6), 127.1 (Ph C-4), 129.5 (Ph C-3,5), 132.7 (C-5, ^1J=194.0 Hz), 139.3 (Ph C-1), 157.7 (C-3, ^3J(C3,H5)=9.7 Hz), 167.7 (CO, ^2J(CO,CH_3)=7.1 Hz); ^{15}N NMR (50 MHz, $CDCl_3$): δ −171.7 (N1), N-2 was not found; IR (KBr): 3139 (CH_{arom}), 1759 (C=O), 1531, 1457, 1225, 1190, 887, 761, 689 cm^{-1}; MS *m*/*z* (%): 328 (M$^+$, 5), 286 (100), 77 ($C_6H_5^+$, 53). Anal. Calcd for $C_{11}H_9IN_2O_2$: C, 40.27; H, 2.76; N, 8.54. Found: C, 40.19; H, 2.70, N, 8.39.

References and notes

1. (a) Yang, L.; Okuda, F.; Kobayashi, K.; Nozaki, K.; Tanabe, Y.; Ishii, Y.; Haga, M. *Inorg. Chem.* **2008**, *47*, 7154; (b) Chang, S.-Y.; Chen, J.-L.; Chi, Y. *Inorg. Chem.* **2007**, *46*, 11202; (c) Chang, E.-M.; Lee, C.-T.; Chen, C.-Y.; Wong, F. F.; Yeh, M.-Y. *Aust. J. Chem.* **2008**, *61*, 342; (d) Mukherjee, R. *Coord. Chem. Rev.* **2000**, *206*, 151.
2. (a) Theodoridis, G. In *Modern Crop Protection Compounds*; Krämer, W., Schirmer, U., Eds.; Wiley-VCH: Weinheim, 2007; Vol. 1, pp 153–186; (b) Shiga, Y.; Okada, I.; Ikeda, Y.; Takizawa, E.; Fukuchi, T. *J. Pesticide Sci.* **2003**, *28*, 313; (c) Lindell, S. D.; Moloney, B. A.; Hewitt, B. D.; Earnhaw, C. G.; Philip, P. J.; Dancer, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1985; (d) Vicentini, C. B.; Romagnoli, C.; Andreotti, E.; Mares, D. *J. Agric. Food Chem.* **2007**, *55*, 10331; (e) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Bueno, J.; Villanova, S. *J. Org. Chem.* **2008**, *73*, 8545; (f) Dutra, G. A.; Hamper, B. C.; Mitschke, D. A.; Moedritzer, K.; Rogers, K. D. PCT Int. Appl., WO 8206, 962; *Chem. Abstr.* **1992**, *117*, 69859.
3. (a) Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 3rd ed.; George Thieme: Stuttgart, New York, NY, 1999; pp 1190–1787; (b) Dax, S. L. *Antibacterial Chemotherapeutic Agents*; Blackie Academic and Professional: London: Weinheim, New York, NY, Melbourne, Madras, 1997; 396 pp.
4. Ha-Duong, N.-T.; Dijols, S.; Marques-Soares, C.; Minoletti, C.; Dansette, P. M.; Mansuy, D. *J. Med. Chem.* **2001**, *44*, 3622.
5. de Paulis, T.; Hemstapat, K.; Chen, Y.; Zhang, Y.; Saleh, S.; Alagille, D.; Baldwin, R. M.; Tamagnan, G. D.; Conn, P. J. *J. Med. Chem.* **2006**, *49*, 3332.

6. (a) Bebernitz, G. R.; Argentieri, G.; Battle, B.; Brennan, C.; Balkan, B.; Burkey, B. F.; Eckhard, M.; Gao, J.; Kapa, P.; Strohschein, R. J.; Schuster, H. F.; Wilson, M.; Xu, D. D. *J. Med. Chem.* **2001**, *44*, 2601; (b) Raufl, M.; König, W. *Immunopharmacology* **1990**, *19*, 103.
7. Ahrens, H.; Koch, H.; Schroder, E.; Biere, H.; Kapp, J.-F. U.S. Patent, 4,042,706.
8. (a) Letendre, L.; McGhee, W. D.; Snoddy, C.; Klemm, G.; Gaud, H. T., WO 03/09974 A1; (b) Oh, L. M. *Tetrahedron Lett.* **2006**, *47*, 7943.
9. (a) El-Emary, T.; Abdel-Mohsen, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 2459; (b) Farghaly, A.-R.; El-Kashef, H. *Arkivoc* **2006**, *xi*, 76.
10. Staufer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *43*, 4934.
11. (a) Kost, A. N.; Grandberg, I. I. Progress in Pyrazole Chemistry. In *Advances in Heterocyclic Chemistry*; Katrizky, A. R., Boulton, A. J., Eds.; Academic: New York, NY, 1966; pp 347–429; (b) Elquero, J. Pyrazoles and their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, p 167; (c) Luo, Y.; Potvin, P. G. *J. Org. Chem.* **1994**, *59*, 1761; (d) Gosselin, F.; O'Shea, P. D.; Webster, R. A.; Reamer, R. A.; Tillyer, R. D.; Grabowski, E. J. J. *Synlett* **2006**, 3267.
12. (a) Finar, I. L.; Hurlock, R. J. *J. Chem. Soc., Chem. Commun.* **1957**, 3024; (b) Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8862; (c) Maheswaran, H.; Krishna, G. G.; Prasanth, K. L.; Srinivas, V.; Chaitanya, G. K.; Bhanuprakash, K. *Tetrahedron* **2008**, *64*, 2471; (d) Jitchati, R.; Batsanov, A. S.; Bryce, M. R. *Tetrahedron* **2009**, *65*, 855.
13. (a) Wang, X. J.; Tan, J.; Zhang, L. *Org. Lett.* **2000**, *2*, 3107; (b) Bouabdallah, I.; Touzani, R.; Zidane, I.; Ramdani, A.; Radi, S. *Arkivoc* **2006**, *xii*, 138; (c) Elguero, J.; Marzin, C.; Linda, P.; Katrizky, A. R. *Advances in Heterocyclic Chemistry, Supplement I: The Tautomerism of Heterocycles*; Academic: New York, NY, 1976; pp 313–336; (d) Holzer, W.; Kautsch, C.; Laggner, C.; Claramunt, R. M.; Pérez-Torralba, M.; Alkorta, I.; Elguero, J. *Tetrahedron* **2004**, *60*, 6791.
14. (a) Zhang, J.; Didierlaurent, S.; Fortin, M.; Lefrancois, D.; Uridat, E.; Vevert, J. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2575; (b) Organ, M. G.; Mayer, S. *J. Comb. Chem.* **2003**, *5*, 118; (c) Dvorak, C. A.; Rudolph, D. A.; Ma, S.; Carruthers, N. I. *J. Org. Chem.* **2005**, *70*, 4188; (d) Dragovich, P. S.; Bertolini, T. M.; Ayida, B. K.; Li, L.-S.; Murphy, D. E.; Ruebsam, F.; Sun, Z.; Zhou, Y. *Tetrahedron* **2007**, *63*, 1154; (e) Guillou, S.; Nesmes, O.; Ermolenko, M. S.; Janin, Y. L. *Tetrahedron* **2009**, *65*, 3529.
15. (a) Gérard, A.-L.; Bouillon, A.; Mahatsekake, C.; Collot, V.; Rault, S. *Tetrahedron Lett.* **2006**, *47*, 4665; (b) Ralph, J. M.; Faigt, T. H.; Silva, D. J.; Feng, Y.; Blackledge, C. W.; Adams, J. L. *Tetrahedron Lett.* **2009**, *50*, 1377; (c) Kudo, M.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282.
16. Bourrain, S.; Ridgill, M.; Collins, I. *Synlett* **2004**, 795.
17. Wang, X.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* **2000**, *41*, 4713.
18. Koenig, H.; Goetz, N.; Klein, U.; Eller, K. WO 9703969, 1997; *Chem. Abstr.* **1997**, *126*, 199566.
19. Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.
20. O'Brien, D. F.; Gates, J. W., Jr. *J. Org. Chem.* **1966**, *31*, 1538.
21. Kim, M. M.; Ruck, R. T.; Zhao, D.; Huffman, M. A. *Tetrahedron Lett.* **2008**, *49*, 4026 and references cited therein.
22. Roy, S.; Gribble, G. W. *Synth. Commun.* **2006**, *36*, 3487.
23. Nedzelskyte, E.; Martynaitis, V.; Sackus, A.; Eller, G. A.; Holzer, W. *Molbank* 2007, M551; *Chem. Abstr.* **2007**, *149*, 378603.
24. Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2485.
25. Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.
26. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
27. (a) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
28. Wawrzyniak, P.; Heinicke, J. *Tetrahedron Lett.* **2006**, *47*, 8921 and references cited therein.
29. Kocienski, P. J. *Protecting Groups*; Georg Thieme: Stuttgart, New York, NY, 2004; pp 323–364.
30. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
31. IJpeij, E. G.; Beijer, F. H.; Arts, H. J.; Newton, C.; de Vries, J. G.; Gruter, G.-J. M. *J. Org. Chem.* **2002**, *67*, 169.
32. Sokolyuk, N. T.; Pisulina, L. P.; V'yugin, A. I. *Russ. J. Org. Chem.* **2002**, *38*, 95.
33. Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
34. Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12664.
35. Kerr, J. A. *Chem. Rev.* **1966**, 465.
36. Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 10030.
37. Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657.
38. Portions of this work were presented at the 15th European Symposium on Organic Chemistry, Dublin, Ireland, July 2007 (poster No. 198, book of abstracts p 262) and at the 41st IUPAC World Chemistry Congress, Torino, Italy, August 2007 (poster No. S08P92, book of abstracts p 217).
39. Ahrens, H.; Biere, H.; Rufer, C.; Schroeder, E.; Koch, H. DE 2347015, 1975; *Chem. Abstr.* **1975**, *83*, 58815.
40. Bratenko, M. K.; Chornous, V. A.; Vvok, M. V. *Khim. Geterotsikl. Soedin.* **2002**, 1311; *Chem. Heterocycl. Compd.* **2002**, *38*, 1156.
41. Padwa, A.; Gehrlein, L. *J. Heterocycl. Chem. (Engl. Transl.)* **1975**, *12*, 589.