JOC The Journal of Organic Chemistry

Article

Palladium-catalyzed chelation-assisted regioselective oxidative dehydrogenative homocoupling/ortho-hydroxylation in N-phenylpyrazoles

Harikrishna Batchu, Soumya Bhattacharyya, Ruchir Kant, and Sanjay Batra

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b00733 • Publication Date (Web): 07 Jul 2015

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Palladium-catalyzed chelation-assisted regioselective oxidative dehydrogenative homocoupling/*ortho*-hydroxylation in *N*-phenylpyrazoles

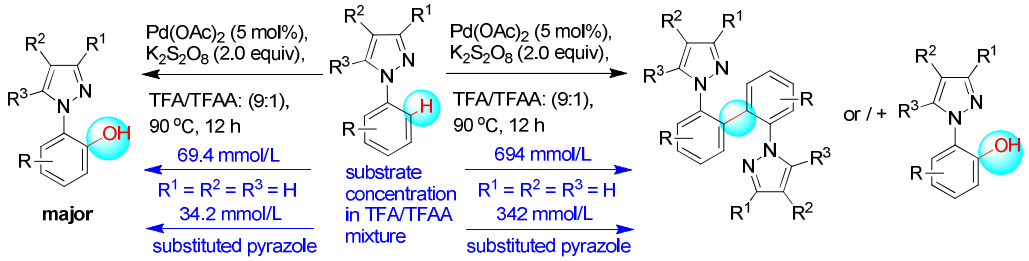
Harikrishna Batchu,[a,†] *Soumya Bhattacharyya,*[a,†] *Ruchir Kant,*[b] *and Sanjay Batra**[a,c]

[a]Medicinal and Process Chemistry Division and [b]Molecular and Structural Biology Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, Uttar Pradesh, India

[c]Academy of Scientific and Innovative Research, New Delhi 110025

batra_san@yahoo.co.uk, s_batra@cdri.res.in

RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)



ABSTRACT. A Palladium-catalyzed pyrazole-directed regioselective oxidative C(sp2)-H-functionalization of the *N*-phenyl ring in *N*-phenylpyrazoles to afford either a biaryl bis-pyrazole (via dehydrogenative homocoupling) or *N*-(*ortho*-hydroxyphenyl)pyrazole (via C-H oxygenation) or their

mixture is described. The substitutions on the *N*-phenyl ring and the pyrazole ring and the dilution of the reaction medium with respect to TFA:TFAA mixture (substrate concentration) have remarkable influence on the outcome of the reaction. It was discovered that if the reactions were performed under highly dilute conditions (*ca* 10 times), *N*-(*ortho*-hydroxyphenyl)pyrazoles were the major or the sole products.

KEYWORDS. Palladium, pyrazole, oxidative C-H functionalization, dehydrogenative homocoupling, C-H oxygenation.

Introduction

The pyrazole nucleus, a privileged heteroarene, is encountered in several pharmaceutical agents including Viagra, Crizotinib, Lexiscan, and Celebrex.[1] In addition, many differently substituted pyrazole derivatives are endowed with diverse pharmacological properties.[2] Given such immense significance, there is continuing interest in development of new or alternative synthetic approaches toward efficient synthesis of substituted pyrazoles.[3] We have an ongoing program for formulating general routes to pyrazole derivatives of biological significance.[4] During the course of this work we noticed that recently several compounds bearing 1-(2-hydroxyphenyl)-pyrazole subunit were reported to be useful as antifungal agents **I**,[5] anti-trichophytic adhesive patch,[6] treatment of dermatophytosis and N-type Ca-channel blockers **II**,[7] β-secretase inhibitors **III**[8] and Cu(II) complexing ligandoside in DNA **IV**[9] (Fig. 1). Established routes to their synthesis required starting reactants bearing the hydroxyl group which were either used directly or in the protected form. In principle, the *ortho*-hydroxyl group in the phenyl ring of 1-phenylpyrazole could be readily installed via transition metal-catalyzed ligand assisted *ortho*-directed oxidative C(sp2)-H functionalization.

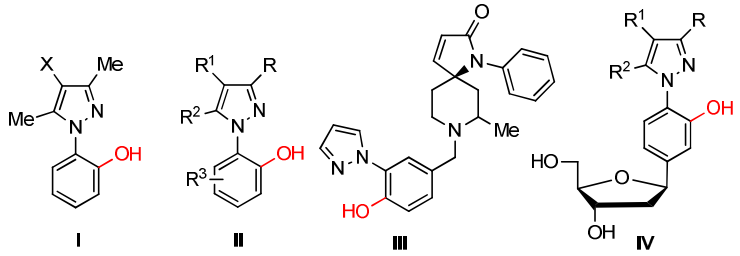


Figure 1. A few recently reported 1-(2-hydroxyphenyl)pyrazole-based bioactive compounds.

During the last decade, transition metal-catalyzed ligand-assisted *ortho*-directed oxidative C–H bond cleavage to accomplish regioselective functionalization of otherwise unreactive C–H bonds in aromatic molecules has been of considerable interest to synthetic organic chemistry.[10-11] These transformations are considered to be green, sustainable and efficient as they do not require preactivation of the substrate. Often such transformations are catalyzed by rhodium, ruthenium, platinum, palladium, copper, nickel and cobalt catalysts but palladium-catalysts are more widely investigated due to several advantages that they offer.[11] Among these reactions, metal-catalyzed oxidative functionalization of C(sp2)-H bond proceed regioselectively with the assistance of many directing groups including pyridine, triazole and several other aza-heterocycles, oxime, imine, amidine, ester, amide, ketone, phenol, and carboxylic acid. The approach has been effectively exploited to install aryl, alkyl, alkenyl, benzyl, hydroxy, acetoxy, alkoxy, amide, trifluoromethyl, azide, nitro, nitrile and halogen groups at proximal C-H bond to the directing group. Amongst the aza-heterocycles, 1-phenylpyrazole has been widely exemplified to undergo ligand-assisted oxidative C(sp2)-H functionalization for introducing some of the aforementioned groups.[12] Intriguingly, the transition metal-catalyzed C-O bond formation in 1-phenylpyrazoles is limited to acetoxy and alkoxy groups and the oxygenation reaction leading to 1-(2-hydroxyphenyl)pyrazole exclusively has yet not been demonstrated. Sanford et al.[12a,c] in their pioneering work on palladium-catalyzed ligand assisted acetoxylation disclosed *ortho*-acetoxylation of the phenyl ring in 1-phenylpyrazole. More recently, Kim et al. extended the palladium-catalyzed acetoxylation of the *ortho*-positions of different phenyl rings present in the pyrazole derivative.[12t] They summarized that the quantity of $PhI(OAc)_2$ influenced the degree of acetoxylation in the products

formed. During investigations of the scope of palladium-catalyzed *ortho*-alkoxylation of 2-aryl-1,2,3-triazoles, Shi and Kuang reported that 1-phenylpyrazole resulted into the formation of 1-(2-hydroxy-6-methoxy)phenyl pyrazole in 42% yield.[13] Hence we sought probing the palladium-catalyzed *ortho*-hydroxylation of the phenyl ring in substituted 1-phenylpyrazoles and found that the success of reaction in these substrates is remarkably influenced by the nature of substitutions present on the phenyl ring and the pyrazole ring and the substrate concentration in TFA:TFAA (9:1) mixture under which the reaction was performed. Herein we present the details of our study in this direction.

Results and Discussion

The study commenced by probing a few reported methods for the palladium-mediated hydroxylation using 1-phenylpyrazole **1a** as the model substrate. Accordingly **1a** (0.25 g, 1.74 mmol) was first treated with $Pd(OAc)_2$ (10 mol%), oxone (2.0 equiv), Cs_2CO_3 (2.0 equiv), in DMF (5 mL) at 120 ^oC for 24 h but the starting material was recovered unreacted (Scheme 1).[14a] Next, **1a** was treated with $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (4.0 equiv), TFA (0.5 equiv) in dichloroethane but this reaction too failed.[13] However it was gratifying to note that when **1a** was reacted with $Pd(OAc)_2$ (5 mol%), $K_2S_2O_8$ (2.0 equiv), TFA:TFAA (9:1, v/v) (2.5 mL) at 90 ^oC for 12 h, a solid product in 68% yield was isolated after the work up.[15,14b] Against our anticipation, the structure of the product was delineated as 2,2'-di(1*H*-pyrazol-1-yl)biphenyl (**3a**) instead of 1-(2-hydroxyphenyl)-pyrazole **2a**. The formation of **3a** was attributed to the oxidative dehydrogenative homocoupling by cleavage of the *ortho* C-H bond. Notably such dehydrogenative homocoupling in 1-phenylpyrazole was earlier reported in the presence of rhodium or ruthenium catalysts[16] but was unprecedented for the palladium catalyst. Therefore we considered optimizing the reaction with palladium catalyst and examine its scope. As a result several combinations of $Pd(OAc)_2$ and oxidants including $Na_2S_2O_8$, molecular oxygen, benzoylperoxide, and TBHP were screened and the results are summarized in Table 1. It is evident from Table 1 that $Pd(OAc)_2$ in combination with $K_2S_2O_8$ or oxone offer superior yields of **3a** but the reaction in the presence of $K_2S_2O_8$ was relatively fast (entries 1-2). In contrast $Na_2S_2O_8$, benzoylperoxide, and TBHP afforded **3a** in low yield while reaction failed under molecular oxygen (entries 3-6). It is worth

mentioning that during compilation of this work Sun et al.[17] reported palladium-catalyzed aryl C(sp2)–H bond hydroxylation of 2-arylpyridine in dichloroethane using TBHP as the sole oxidant but this condition did not work in our hand for transforming **1a** to **2a** or **3a** (entry 10). Thus the condition that offered best yield of **3a** was heating **1a** (0.25 g at a concentration of 694 mmol/L), $Pd(OAc)_2$ (5 mol%), $K_2S_2O_8$ (2.0 equiv) in TFA:TFAA (9:1, v/v) at 90 °C for 12 h.

Scheme 1. Results of initial reactions explored for oxidative C(sp2)-H hydroxylation in the phenyl ring in 1-phenylpyrazole **(1a)**

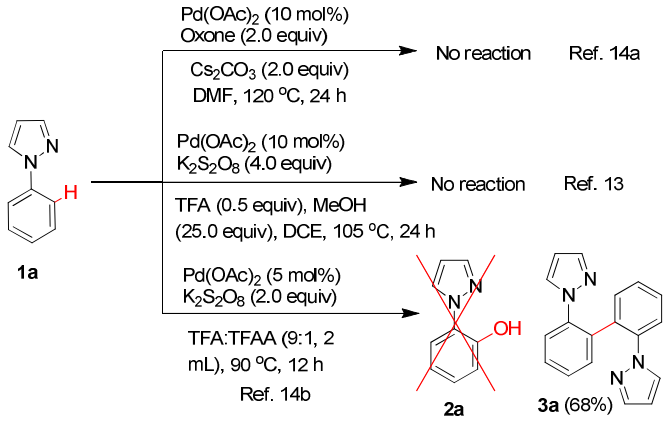
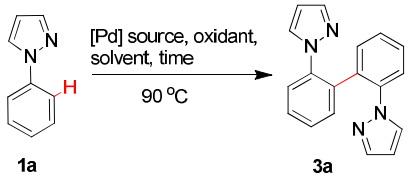


Table 1. Optimization[a] of the palladium-catalyzed oxidative dehydrogenative homocoupling with 1-phenylpyrazole **1a** leading to biaryl bis-pyrazole **3a**



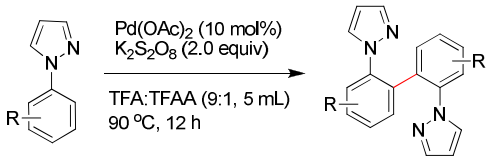
entry	catalyst (mol%)	solvent	oxidant (equiv)	time (h)	yield **3a** (%)[b]
1	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	oxone (2.0)	24	62
2	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	$K_2S_2O_8$ (2.0)	12	68
3	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	$Na_2S_2O_8$ (2.0)	24	27
4	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	O_2 (balloon)	24	-
5	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	benzoyl peroxide (2.0)	24	20

6	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	TBHP (2.0)	24	7
7[b]	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	$K_2S_2O_8$ (1.5)	24	55
8[b]	$Pd(OAc)_2$ (5)	TFA	$K_2S_2O_8$ (2.0)	24	34
9	$Pd(OAc)_2$ (5)	TFAA	$K_2S_2O_8$ (2.0)	24	trace
10	$Pd(OAc)_2$ (5)	DCE	TBHP (6.0)	24	trace

[a]All reactions were performed using 0.25 g of pyrazole **1a** at a concentration of 694 mmol/L of solvent, [b]Yields of chromatographically pure product.

With optimized conditions in hand, we set out to test the scope of the methodology for a variety of 1-(substitutedphenyl)pyrazoles **(1b-1q)** and the results are presented in Scheme 2. It was observed that in all cases except for **1l** and **1q**, the corresponding biaryl bis-pyrazoles were isolated. Whereas the substrates carrying *ortho*- and *para*-substitution on the phenyl ring **(1b-e, 1h-k, 1m-n)** produced the corresponding products **3b-e, 3h-k, 3m-n** in good yields, the ones with *meta*-substitutions **(1f** and **1g)** furnished the respective products **3f** and **3g** in moderate yields only. Further, pyrazoles **1o** and **1p** bearing dimethyl-substituted phenyl ring also furnished **3o** and **3p**, respectively in good yields. The structure of the biaryl bis-pyrazole was unambiguously secured by the X-ray crystallographic analysis of crystal of **3p** obtained from hexanes: EtOAc (see Supporting Information). It is speculated that failure of reaction in pyrazole **1l** could be due to the electron donating character of the methoxy group whereas failure of reaction in pyrazole **1q** bearing *N*-naphth-2-yl group may be because of steric constraint towards the formation of **3q**. In order to ascertain the limitation of scope for substrates bearing electron rich phenyl ring, we examined the reaction of 1-(3-methoxyphenyl)pyrazole **(1r)** and found that this substrate too failed to react under the optimized conditions. The formation of **3** can be readily explained on the basis of mechanism involving Pd (IV) species as proposed by Sanford et al. (vide infra). The scope of the protocol was also tested with 1-benzylpyrazole **(4)** but this substrate failed to react under the standardized conditions (Scheme 3).

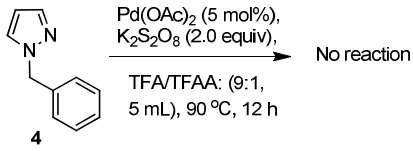
Scheme 2. Scope of ligand-assisted palladium-catalyzed oxidative dehydrogenative homocoupling to produce biaryl bis-pyrazoles in 1-(substituted phenyl)pyrazoles[a,b]



1a	R = H	**3a**	R = H (68%)
1b	R = 2-Cl	**3b**	R = 2-Cl (83%)
1c	R = 2-Me	**3c**	R = 2-Me (80%)
1d	R = 2-CF_3	**3d**	R = 2-CF_3 (74%)
1e	R = 2-CO_2Et	**3e**	R = 2-CO_2Et (60%)
1f	R = 3-F	**3f**	R = 3-F (45%)
1g	R = 3-Cl	**3g**	R = 3-Cl (48%)
1h	R = 4-F	**3h**	R = 4-F (78%)
1i	R = 4-Cl	**3i**	R = 4-Cl (75%)
1j	R = 4-Br	**3j**	R = 4-Br (70%)
1k	R = 4-Me	**3k**	R = 4-Me (72%)
1l	R = 4-OMe	**3l**	R = 4-OMe (0%)
1m	R = 4-CF_3	**3m**	R = 4-CF_3 (74%)
1n	R = 4-CO_2Et	**3n**	R = 4-CO_2Et (72%)
1o	R = 2,4-Me_2	**3o**	R = 2,4-Me_2 (74%)
1p	R = 3,4-Me_2	**3p**	R = 3,4-Me_2 (70%)
1q	R = naphth-2-yl	**3q**	R = naphth-2-yl (0%)
1r	R = 3-OMe	**3r**	R = 3-OMe (0%)

[a]Reactions were performed with 0.5-0.77 g of pyrazoles **(1a-r)** at a substrate concentration of 694 mmol/L of solvent. [b]Yields after column chromatography.

Scheme 3. Result of the reaction of 1-benzylpyrazole under the optimized condition[a]

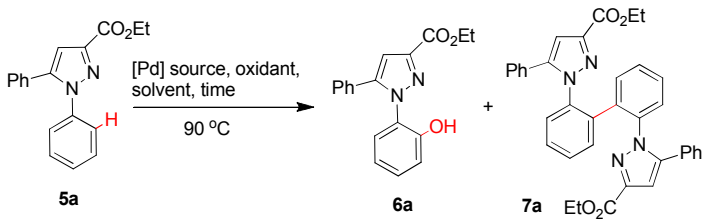


[a]Reaction was performed with 0.55 g of pyrazole **(4)** at a substrate concentration of 694 mmol/L.

After studying the scope of the protocol with unsubstituted pyrazole derivatives, we turned our attention to a variety of substituted 1-phenylpyrazoles. Initially in a pilot experiment ethyl 1,5-diphenyl-1*H*-pyrazole-3-carboxylate (**5a**) (0.25 g) was subjected to reaction with $Pd(OAc)_2$ in TFA:TFAA (9:1, 2.5 mL) under the optimized conditions which upon workup and purification resulted into isolation of the major product in 76% and minor product in 3% yield only. We were pleased to discover that the major product was spectroscopically characterized as ethyl 1-(2-hydroxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate **(6a)** whereas the minor product was identified to be the biaryl bis-pyrazole **7a**. However, it was realized that in this pilot reaction, the substrate concentration of **5a** was 342 mmol/L instead of 694 mmol/L optimized for the unsubstituted pyrazoles **1**. As a consequence, the reaction was repeated with **5a** (0.5 g) at a substrate concentration of 685 mmol/L. Although presence of lower amount of solvent made the reaction too cumbersome to perform, we could isolate the **6a** in 44% and **7a** in 10% yields besides unreacted **5a** and a mixture of unidentified products. Perhaps the presence of substitutions

at 3- and 5-positions in pyrazole **5a** may have induced certain steric constraint thereby favoring the *ortho*-hydroxylation of phenyl ring rather than dehydrogenative homocoupling. In view of our interest to synthesize substituted 1-(2-hydroxyphenyl)pyrazoles exclusively coupled with ease of performing the reaction with optimal solvent amount, we decided performing the reactions of substituted pyrazoles at a substrate concentration of 342 mmol/L. In order to examine the possibility of improving the yields of **6a**, we screened the reaction of **5a** with respect to different palladium sources, oxidants and solvents and the results are summarized in Table 2. Amongst several oxidants evaluated, $K_2S_2O_8$ gave the best result whereas oxone and $PhI(OAc)_2$ gave **6a** in slightly lower yields (compare entry 1 with entries 2, 3). In contrast, the yield of **6a** in the presence of all other oxidants screened for the reaction was found to be inferior (entries 4-7). Reducing the amount of $K_2S_2O_8$ from 2.0 equiv to 1.5 equiv reduced the yield of **6a** appreciably (entry 8). Performing the reaction in the presence of TFA or TFAA individually or any other organic solvent did not afford the required product **6a** in better yields (entries 9-12). Altering the palladium source revealed that $Pd(TFA)_2$ was as effective as $Pd(OAc)_2$ to afford **6a** in 75% yield whereas $Pd(PPh_3)_2Cl_2$ failed to yield any product (entries 13-14). However even in $Pd(TFA)_2$ mediated reaction, the presence of **7a** was detected. Therefore it was concluded to continue to investigate the scope further with the optimized conditions using substrate concentration of 342 mmol/L.

Table 2. Results of the study to examine the effect of different palladium source, oxidants and solvents on the formation of **6a** from **5a**[a]



5a 6a 7a

entry	catalyst (mol%)	solvent	oxidant (equiv)	time (h)	yield **6a** (%)[c]
1	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	$K_2S_2O_8$ (2.0)	12	76[d]
2[b]	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	oxone (2.0)	12	72[d]

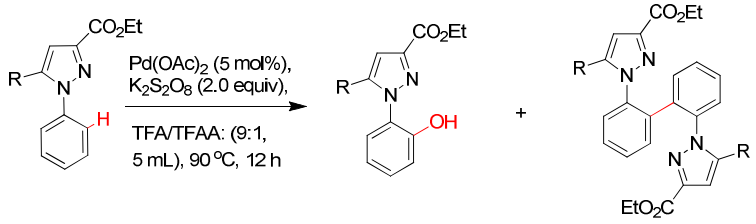
3	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	$PhI(OAc)_2$ (2.0)	12	70
4	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	TBHP (2.0)	24	10
5	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	benzoyl peroxide (2.0)	24	-
6	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	$Na_2S_2O_8$ (2.0)	24	30
7	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	O_2 (ballon)	24	-
8	$Pd(OAc)_2$ (5)	TFA:TFAA (9:1)	$K_2S_2O_8$ (1.5)	24	40[d]
9	$Pd(OAc)_2$ (5)	TFA	$K_2S_2O_8$ (2.0)	24	42[d]
10	$Pd(OAc)_2$ (5)	TFAA	$K_2S_2O_8$ (2.0)	24	-
11	$Pd(OAc)_2$ (5)	IPA	$K_2S_2O_8$ (2.0)	24	-
12	$Pd(OAc)_2$ (5)	DCE	$K_2S_2O_8$ (2.0)	72	20
13	$Pd(PPh_3)_2Cl_2$ (5)	TFA:TFAA (9:1)	$K_2S_2O_8$ (2.0)	12	-
14	$Pd(TFA)_2$ (5)	TFA:TFAA (9:1)	$K_2S_2O_8$ (2.0)	12 h	75[d]

[a]Except for entry 2, all reactions were performed using 0.1 g of pyrazole **(5a**) at a concentration of 342 mmol/L of solvent, [b]Reaction in entry 2 was performed with 0.25 g of **5a** at identical substrate concentration; [c]Yields of chromatographically pure products. [d]2-3% of **7a** was isolated

In next stage of the study, we examined the scope of the reaction with several differently substituted pyrazoles. In the first set, reactions of various ethyl 1,5-diphenyl-1*H*-pyrazole-3-carboxylates (**5b-g**) carrying differently substituted 5-phenyl ring were probed as outlined in Scheme 4. It was observed that in each case substituted 1-(2-hydroxyphenyl)pyrazole **6b-d,f-g** and biaryl bis-pyrazole **7b-d,f-g** were isolated in variable ratio but for the compound **5e** bearing 4-methyl substituent, 1-(2-hydroxyphenyl)pyrazole derivative **6e** was isolated as the major product. Further substrate **5h** bearing 3,4-dimethyl group too furnished the product as isolable mixture of **6h** and **7h**, but the 3,4,5-trimethoxy phenyl ring bearing substrate **5i** afforded **6i** exclusively. In the next stage we focused on substrate-set bearing different substitutions in the *N*-phenyl ring and unsubstituted 5-phenyl ring as presented in Scheme 5. Accordingly pyrazoles **5j-p** were subjected to the palladium-catalyzed reaction and it was found that all substrates **(5k-n,p)**, except for **5j, 5o** with *ortho*-substituted *N*-phenyl ring, furnished a mixture of substituted 1-(2-hydroxyphenyl)pyrazoles **6k-n,p** and biaryl bis-pyrazoles **7k-n,p**. It seems

that the presence of *ortho*-substituent in **5j** and **5o** offered resistance to chelation leading to the failure of reaction. The structures for 1-(2-hydroxyphenyl)pyrazoles **6** and biaryl bis-pyrazoles **7** were secured by performing the X-ray crystallographic analysis of representative compounds **6l** (hexanes: EtOAc) and **7b** ($CHCl_3$: MeOH) (See Supporting Information).

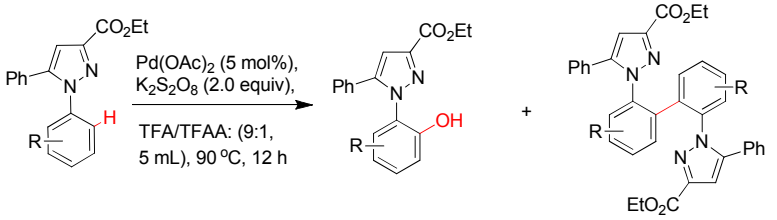
Scheme 4. Results of the study of scope of the protocol for C-hydroxylation with substituted 5-substitutedphenyl-1-phenyl-1*H*-pyrazole-3-carboxylates **(5a-5i)**[a,b]



5a R = Ph	**6a** R = Ph (76%)	**7a** R = Ph (3%)
5b R = 2-Cl-C_6H_4	**6b** R = 2-Cl-C_6H_4 (45%)	**7b** R = 2-Cl-C_6H_4 (29%)
5c R = 4-F-C_6H_4	**6c** R = 4-F-C_6H_4 (70%)	**7c** R = 4-F-C_6H_4 (12%)
5d R = 4-Cl-C_6H_4	**6d** R = 4-Cl-C_6H_4 (44%)	**7d** R = 4-Cl-C_6H_4 (28%)
5e R = 4-Me-C_6H_4	**6e** R = 4-Me-C_6H_4 (74%)	**7e** R = 4-Me-C_6H_4 (8%)
5f R = 4-OMe-C_6H_4	**6f** R = 4-OMe-C_6H_4 (40%)	**7f** R = 4-OMe-C_6H_4 (32%)
5g R = 4-NO_2-C_6H_4	**6g** R = 4-NO_2-C_6H_4 (35%)	**7g** R = 4-NO_2-C_6H_4 (20%)
5h R = 2,4-Me_2-C_6H_3	**6h** R = 2,4-Me_2-C_6H_3 (44%)	**7h** R = 2,4-Me_2-C_6H_3 (30%)
5i R = 3,4,5-$(OMe)_3$-C_6H_2	**6i** R = 3,4,5-$(OMe)_3$-C_6H_2 (72%)	**7i** R = 3,4,5-$(OMe)_3$-C_6H_2 (0%)

[a]Reactions were performed with 0.5-0.65 g of pyrazoles **(5a-i)** at a substrate concentration of 342 mmol/L of solvent. [b]Yields after column chromatography.

Scheme 5. Results of the study of scope of the protocol for C-hydroxylation with substituted 5-phenyl-1-substituted phenyl-1*H*-pyrazole-3-carboxylates **(5j-5p)**[a,b]



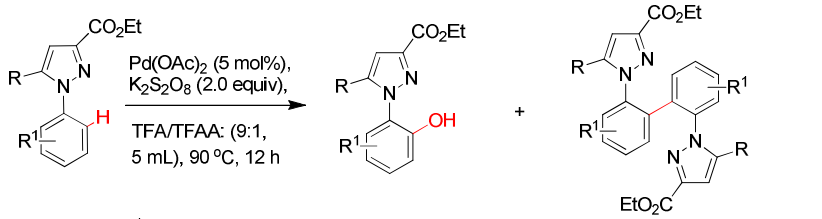
5j R = 2-Cl	**6j** R = 2-Cl (0%)	**7j** R = 2-Cl (0%)
5k R = 3-Cl	**6k** R = 3-Cl (78%)	**7k** R = 3-Cl (10%)
5l R = 4-F	**6l** R = 4-F (41%)	**7l** R = 4-F (24%)
5m R = 4-Cl	**6m** R = 4-Cl (48%)	**7m** R = 4-Cl (22%)
5n R = 4-Br	**6n** R = 4-Br (40%)	**7n** R = 4-Br (22%)
5o R = 2,5-Me_2	**6o** R = 2,5-Me_2 (0%)	**7o** R = 2,5-Me_2 (0%)
5p R = 3,4-Me_2	**6p** R = 3,4-Me_2 (38%)	**7p** R = 3,4-Me_2 (20%)

[a]Reactions were performed with 0.53-0.63 g of pyrazoles **(5j-p)** at a substrate concentration of 342 mmol/L. [b]Yields after column chromatography.

Following these results, we considered investigating the protocol using ethyl 1-substituted phenyl-5-alkyl-1*H*-pyrazole-3-carboxylates **8a-g** as the starting substrates (Scheme 6). In the first set the reactions

of 1-substituted phenyl-5-methyl-1*H*-pyrazole-3-carboxylates **8a-e** were examined which under the standardized conditions produced the corresponding 1-(2-hydroxyphenyl)pyrazoles **9a-e** only with no trace of biaryl bis-pyrazoles **10a-e**. Replacing the methyl group with propyl or isopropyl groups **(8f-g)**, however resulted in the formation of a mixture of 1-(2-hydroxyphenyl)pyrazoles **9f-g** and biaryl bis-pyrazoles **10f-g** in approximately 2:1 ratio. Further, we discovered that if the 5-position in pyrazole ring was left unsubstituted as in **8h** then only the biaryl product **10h** was isolated with no trace of **9h**.

Scheme 6. Results of the study of scope of the protocol for C-hydroxylation with ethyl 1-substitutedphenyl-5-alkyl-1*H*-pyrazole-3-carboxylates **(8a-g)**[a,b]



8a R = Me, R^1 = H
8b R = Me, R^1 = 3-Cl
8c R = Me, R^1 = 4-F
8d R = Me, R^1 = 4-Br
8e R = Me, R^1 = 4-Me
8f R = ^{n}Pr, R^1 = H
8g R = ^{i}Pr, R^1 = H
8h R = H, R^1 = H

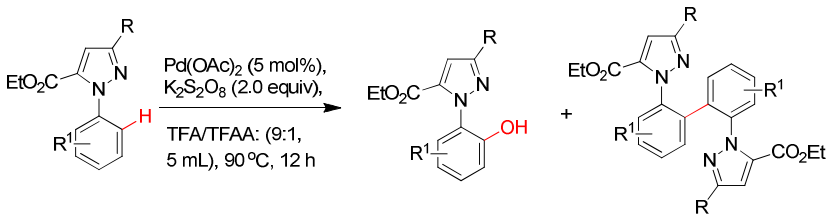
9a R = Me, R^1 = H (74%)
9b R = Me, R^1 = 3-Cl (74%)
9c R = Me, R^1 = 4-F (72%)
9d R = Me, R^1 = 4-Br (75%)
9e R = Me, R^1 = 4-Me (73%)
9f R = ^{n}Pr, R^1 = H (35%)
9g R = ^{i}Pr, R^1 = H (42%)
9h R = H, R^1 = H (0%)

10a R = Me, R^1 = H (0%)
10b R = Me, R^1 = 3-Cl (0%)
10c R = Me, R^1 = 4-F (0%)
10d R = Me, R^1 = 4-Br (0%)
10e R = Me, R^1 = 4-Me (0%)
10f R = ^{n}Pr, R^1 = H (18%)
10g R = ^{i}Pr, R^1 = H (20%)
10h R = H, R^1 = H (80%)

[a]Reactions were performed with 0.37-0.53 g of pyrazoles **(8a-h)** at a substrate concentration of 342 mmol/L. [b]Yields after column chromatography.

Subsequently, we examined the scope of the methodology with substituted pyrazoles **(11a-c** and **14a-d)** bearing carboxylate group at C-5 and C-4 position, respectively. It was observed in the first subset **11a-c**, whereas **11a-b** afforded the biaryl bis-pyrazoles **13a-b** exclusively in 70-72% yields, **11c** was recovered unreacted under the optimized conditions (Scheme 7). In lieu of these results, it was speculated that the presence of phenyl ring at 3-position as in **11c** interfered with the stabilization of the palladium complex. Likewise for ethyl 5-methyl-1-substituted phenyl-1*H*-pyrazole-4-carboxylates **14a-d**, it was found that whereas **14a** and **14b** furnished **16a** and **16b**, respectively, **14c-d** failed to react due to the presence of *ortho*-substituted *N*-phenyl ring (Scheme 8).

Scheme 7. Results of the study of scope of the protocol for C-hydroxylation with ethyl 1-(substituted)phenyl-1*H*-pyrazole-5-carboxylate **(11a-c)**[a,b]



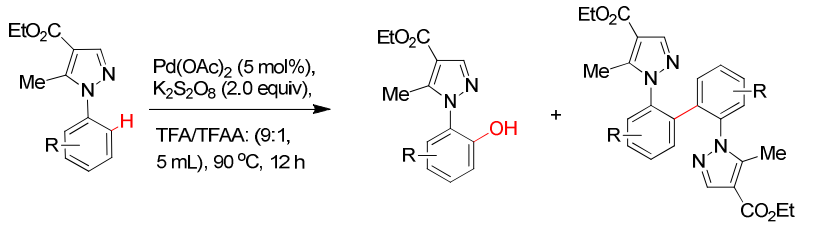
11a R = H, R^1 = H
11b R = H, R^1 = 4-Br-C_6H_4
11c R = Ph, R^1 = H

12a R = H, R^1 = H (0%)
12b R = H, R^1 = 4-Br-C_6H_4 (0%)
12c R = Ph, R^1 = H (0%)

13a R = H, R^1 = H (72%)
13b R = H, R^1 = 4-Br-C_6H_4 (70%)
13c R = Ph, R^1 = H (0%)

[a]Reactions were performed with 0.37-0.5 g of pyrazoles **(11a-c)** at a substrate concentration of 342 mmol/L. [b]Yields after column chromatography.

Scheme 8. Results of the study of scope of the protocol for C-hydroxylation with ethyl 5-methyl-1-(substituted)phenyl-1*H*-pyrazole-4-carboxylate **(14a-d)**[a,b]



14a R = H
14b R = 4-Br
14c R = 2-Me
14d R = 2,4-Cl_2

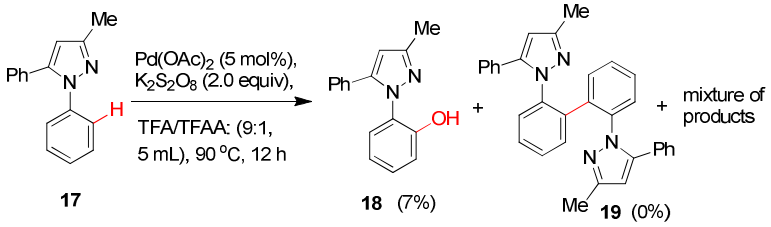
15a R = H (0%)
15b R = 4-Br (0%)
15c R = 2-Me (0%)
15d R = 2,4-Cl_2 (0%)

16a R = H (78%)
16b R = 4-Br (80%)
16c R = 2-Me (0%)
16d R = 2,4-Cl_2 (0%)

[a]Reactions were performed with 0.39-0.52 g of pyrazoles **(14a-d)** at a substrate concentration of 342 mmol/L. [b]Yields after column chromatography.

Finally we investigated the protocol with 3-methyl-1,5-diphenyl-1*H*-pyrazole **17** and found that this substrate resulted in a complex mixture of products from which we could isolate the 1-(2-hydroxyphenyl)pyrazole **(18)** product in 7% yield only (Scheme 9). In addition 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **(20)** was also investigated but this substrate failed to react under the optimized conditions (Scheme 10).

Scheme 9. Reaction of 3-methyl-1,5-diphenyl-1*H*-pyrazole[a,b]



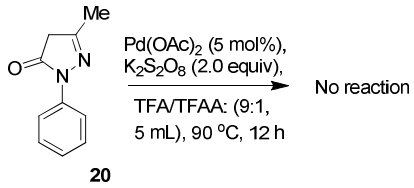
17

18 (7%)

19 (0%)

[a]Reaction was performed with 0.4 g of pyrazole **(17)**. [b]Yield after column chromatography.

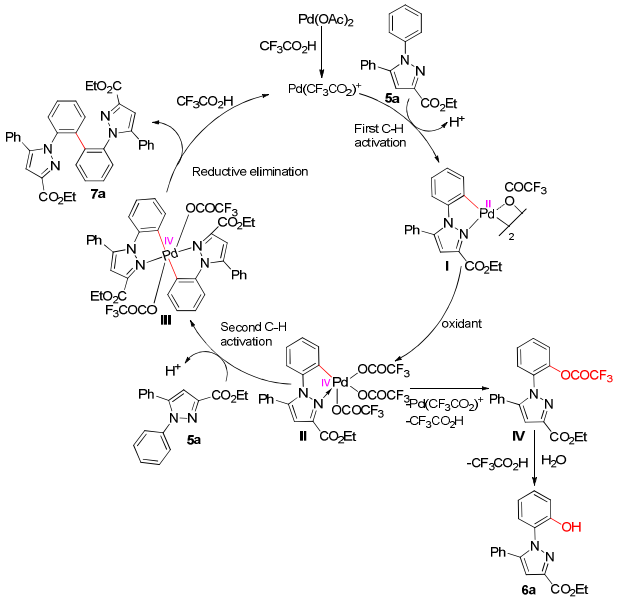
Scheme 10. Reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one



[a]Reaction was performed with 0.3 g of pyrazole **20** at a substrate concentration of 342 mmol/L.

The plausible mechanism for the reaction with **5a** as the model substrate is delineated in Scheme 11. As proposed by Sanford et al. the first C-H activation event in **5a** takes place at the Pd (II) stage leading to the formation of a five membered cyclo-palladium (II) dimeric intermediate **I** which under the reaction conditions, gets oxidized to Pd(IV) intermediate **II**. A second C-H activation event at the Pd (IV) stage would result into the formation of intermediate **III** which on reductive elimination, gives biaryl bis-pyrazole **7a**. In contrast, if the second molecule of the **5a** is not activated to attack the intermediate **II**, then there is a likelihood that reductive elimination may occur to afford the intermediate **IV** that during aqueous workup furnish the substituted *ortho*-hydroxyphenyl pyrazole **6a**.

Scheme 11. Plausible mechanism

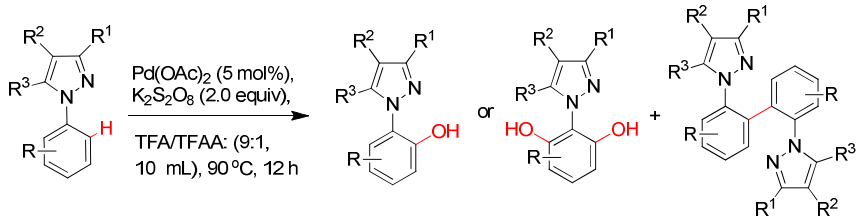


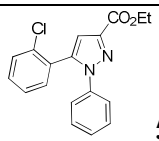
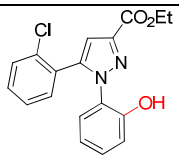
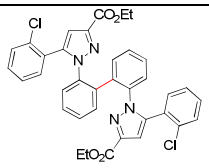
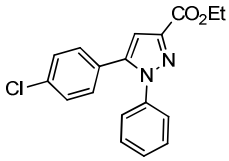
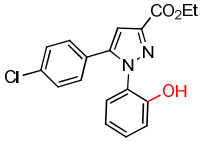
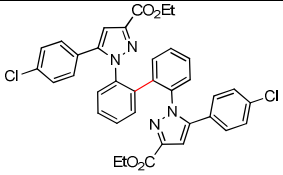
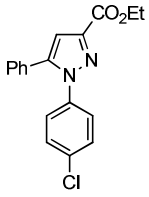
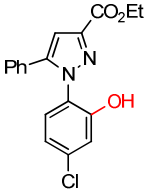
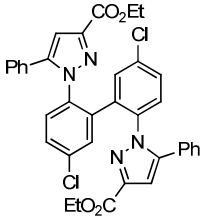
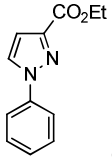
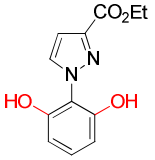
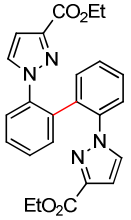
Based on the proposed mechanism and our initial optimization study with pyrazole **5a**, we were prompted to map product formation at different substrate concentration in TFA:TFAA mixture. It was presumed that under dilute conditions the transformation of **II** to **III** may get suppressed driving the

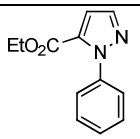
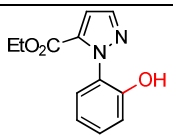
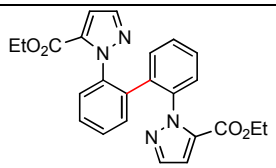
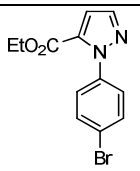
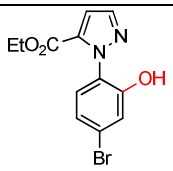
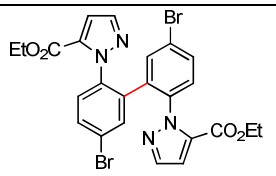
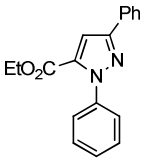
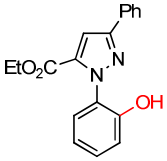
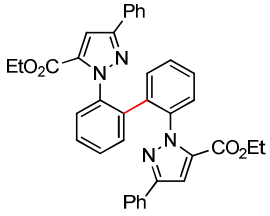
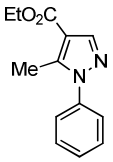
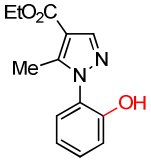
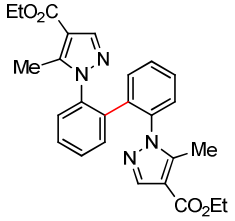
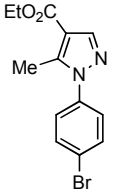
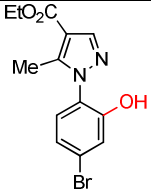
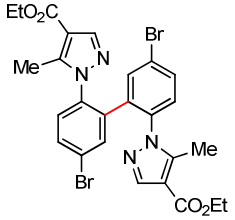
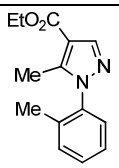
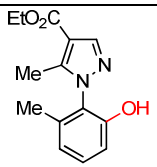
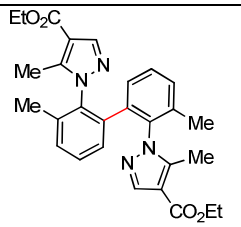
reaction to **IV** thereby producing *ortho*-hydroxylphenyl pyrazole exclusively. In this context, pyrazole **5b** which was known to afford both the products **(6b** and **7b)** in 5:3 ratio was selected as representative compound for the study. Accordingly, **5b** (0.11 g) was treated with $Pd(OAc)_2$ and $K_2S_2O_8$ under the optimized conditions at varying substrate to solvent (TFA:TFAA) concentration of 685 mmol/L to 34.2 mmol/L and the product distribution of the resulting crude mixture of products was monitored via HPLC (see Supporting Information). We were delighted to discover that when the reaction was performed with **5b** at a substrate concentration of 34.2 mmol/L then **6b** was isolated in 68% yield while **7b** was limited to 3% yield (Table 3, entry 1). Encouraged with the success, we tested **5d** and **5m** too under the identical reaction conditions (*ca* 10-folds dilution) and found that these substrates afforded respective **6d** and **6m** as the major products (entries 2, 3). Inspired by this success, we were prompted to examine the substrates from all other series including **8, 11, 14, 17** and **1**. Therefore, first **8h** was subjected to the reaction under dilute conditions and we were pleased to discover that the ethyl 1-(2,6-dihydroxyphenyl)-1*H*-pyrazole-3-carboxylate **21** was isolated in 55% yield beside the biaryl bis-pyrazole **10h** in 20% yield (entry 4). However, when the carboxylate group was present at 5-position in pyrazole as represented by series **11** we found that whereas **11a-b** afforded the biaryl bis-pyrazole exclusively, compound **11c** gave the hydroxy derivative **12c** in trace which could not be isolated but was evident upon detailed LC-MS investigations (entries 5-7). Likewise, for the set of pyrazole bearing carboxylate group at 4-position as represented by **14** we could not detect the presence of corresponding hydroxyphenyl pyrazole product irrespective of dilution (entries 8-11). In contrast for substituted pyrazole **17** we observed that under dilute reaction condition the yield of 1-(2-hydroxyphenyl)pyrazole **(18)** improved to 60% (entry 12). Finally **1a-b, 1e, 1j** as representatives from series **1** which furnished the biaryl bis-pyrazoles **(3)** exclusively were investigated under the altered conditions and it was gratifying to discover that all substrates gave 1-(2-hydroxyphenyl) pyrazoles at a substrate concentration of 69.4 mmol/L. Whereas compound **1b** and **1e** afforded **2b** and **2e**, pyrazoles **1a** and **1j** furnished 2-(1*H*-pyrazol-1-yl)benzene-1,3-diol **22a** and **22j** as the major products in good yields, respectively

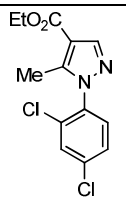
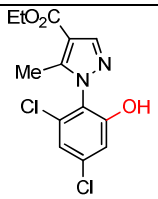
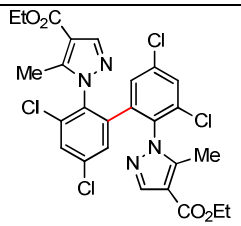
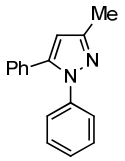
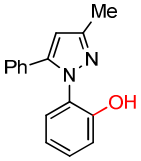
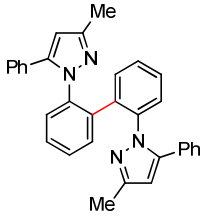
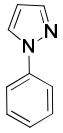
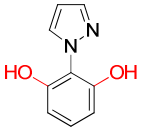
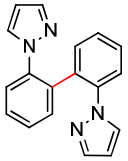
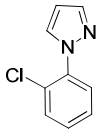
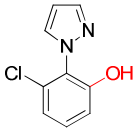
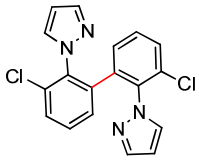
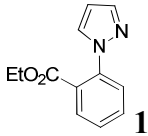
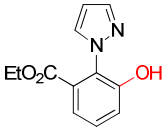
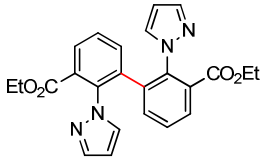
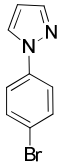
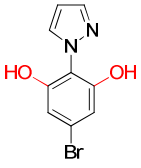
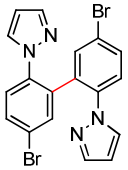
(entries 13-16). These results clearly surmised that *ortho*-hydroxylation in the phenyl ring in *N*-phenyl pyrazoles is favoured when the reaction is performed under excess of TFA:TFA (9:1) mixture.

Table 3. Results of the study towards scope of the protocol for C(sp2)-hydroxylation under dilute conditions



entry	reactant	major product (yield %)[b]	minor product (yield %)[b]
1[a]	 **5b**	 **6b** (71)	 **7b** (3)
2[a]	 **5d**	 **6d** (66)	 **7d** (2)
3[a]	 **5m**	 **6m** (70)	 **7m** (2)
4[a]	 **8h**	 **21** (55)	 **10h** (20)

5[a]	 **11a**	 **12a** (0)	 **13a** (70)
6[a]	 **11b**	 **12b** (0)	 **13b** (65)
7[a]	 **11c**	 **12c** (trace)	 **13c** (0)
8[a]	 **14a**	 **15a** (0)	 **16a** (75)
9[a]	 **14b**	 **15b** (0)	 **16b** (76)
10[a]	 **14c**	 **15c** (0)	 **16c** (0)

11[a]	 **14d**	 **15d** (0)	 **16d** (0)
12[a]	 **17**	 **18** (60)	 **19** (0)
13[b]	 **1a**	 **22a** (60)	 **3a** (3)
14[b]	 **1b**	 **2b** (67)	 **3b** (3)
15[b]	 **1e**	 **2e**(64)	 **3e** (2)
16[b]	 **1j**	 **22b** (62)	 **3j** (3)

[a]Reactions were performed with 0.079-0.112 g of pyrazoles **5, 8**, **14**, **11** or **17** at a substrate concentration of 34.3 mmol/L. [b]Reactions were performed with 0.1-0.15 g of pyrazoles **1** at a substrate concentration of 69.4 mmol/L. [c]Yields after column chromatography.

Conclusions

In summary, we have demonstrated the ligand assisted palladium-catalyzed regioselective oxidative C(sp2)-H activation for dehydrogenative homocoupling and C-H oxygenation reactions in the phenyl ring of substituted 1-phenylpyrazoles. The scope has been explicitly investigated to demonstrate the effect of different substitutions on the outcome of the reaction. It was shown that the set of compounds wherein the pyrazole ring does not bear any substitution under low quantity of TFA:TFAA (9:1, v/v) mixture (higher substrate concentration), afforded the biaryl bis-pyrazoles via dehydrogenative homocoupling exclusively. But the same substrates resulted into the *ortho*-hydroxyphenyl pyrazoles as the major products when the identical reaction was performed in the presence of increased quantity of TFA:TFAA (9:1, v/v) mixture (low substrate concentration). Further in this set of pyrazoles if the phenyl ring carried an *ortho*-substituent then mono-hydroxylation took place but if both the *ortho*-positions were free then bis-hydroxylation prevailed under the conditions. Unlike, in the set of compounds where the pyrazole ring carried carboxylate group at the 3-position in most of the cases a mixture of biaryl bis-pyrazoles and *ortho*-hydroxyphenyl pyrazoles were formed under higher substrate concentration but *ortho*-hydroxyphenyl pyrazoles were isolated in superior yields when the concentration of the starting material was low. In addition for these starting substrates, the protocol worked only when both *ortho*-positions of the phenyl ring were free since all compounds bearing *ortho*-substituted phenyl ring failed to yield any product. Unlike for the pyrazole substrates bearing carboxylate group at the C-5 or C-4 position, mostly biaryl bis-pyrazoles were isolated. Interestingly, for the pyrazoles bearing phenyl group at C-3 position in the place of carboxylate group at lower substrate concentration we could isolate only the *ortho*-hydroxyphenyl pyrazole with no trace of biaryl bis-pyrazoles. Further work to investigate the ligand-assisted C-oxygenation in the phenyl ring in other heterocyclic substrates is underway and would be reported in due course.

Experimental Section

General. All experiments were monitored by analytical thin layer chromatography (TLC) performed on pre-coated silica gel plates. After elution, plate was visualized under UV illumination at 254 nm for

UV active materials. Further visualization was achieved by staining with $KMnO_4$ and charring on a hot plate. Column chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with solvents as indicated. IR spectra were recorded using a FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz spectrometer using TMS as an internal standard (chemical shifts in δ). Peak multiplicities of NMR signals were designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet) etc. The ESI-MS were recorded on Ion Trap Mass spectrometer and the HRMS spectra were recorded as ESI-HRMS on a Q-TOF LC-MS/MS mass spectrometer. Commercial grade reagents and solvents were used without further purification. As **12c** was formed in traces and mapped by LC-MS there is no physical or spectroscopic data (except ESMS) is provided.

The syntheses of different 1-(substitutedphenyl)pyrazoles were carried out according to the literature procedures**.**

1-Phenyl-1*H*-pyrazole (1a).[18]

1-(2-Chlorophenyl)-1*H*-pyrazole (1b).[19]

1-(2-Methylphenyl)-1*H*-pyrazole (1c).[19]

1-(2-(Trifluoromethyl)phenyl)-1*H*-pyrazole (1d).[20]

Ethyl 2-(1*H*-pyrazol-1-yl)benzoate (1e).[21]

1-(3-Fluorophenyl)-1*H*-pyrazole (1f).[22]

1-(3-Chlorophenyl)-1*H*-pyrazole (1g).[23]

1-(4-Fluorophenyl)-1*H*-pyrazole (1h).[23]

1-(4-Chlorophenyl)-1*H*-pyrazole (1i).[23]

1-(4-Bromophenyl)-1*H*-pyrazole (1j).[23]

1-(4-Methylphenyl)-1*H*-pyrazole (1k).[24]

1-(4-Methoxyphenyl)-1*H*-pyrazole (1l).[24]

1-(4-(Trifluoromethyl)phenyl)-1*H*-pyrazole (1m).[24]

Ethyl 4-(1*H*-pyrazol-1-yl)benzoate (1n).[25]

1-(2,4-Dimethylphenyl)-1*H*-pyrazole (1o).[25]

1-(3,4-Dimethylphenyl)-1*H*-pyrazole (1p). Yield: 85 % (1.0 g from 1.5 g); a brown oil; R_f = 0.68 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 2.32 (s, 3H), 6.43 (t, J = 2.2 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 7.37 (dd, J_1 = 8.1 Hz, J_2 = 2.3 Hz, 1H), 7.50 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 1.4 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 19.4, 20.0, 107.3, 116.7, 120.8, 126.8, 130.5, 135.1, 138.4, 140.8. Mass (ESI+) *m/z* = 173.2. ESI-HRMS calcd. for $C_{11}H_{13}N_2$ (M^++H): 173.1079, found: 173.1074.

1-(Naphthalen-2-yl)-1*H*-pyrazole (1q).[26]

1-(3-Methoxyphenyl)-1*H*-pyrazole (1r).[27]

1-Benzyl-1*H*-pyrazole (4).[28]

General procedure for oxidative dehydrogenative homocoupling of *N*-aryl pyrazoles (1a-r) as exemplified for 3a.

A 50 mL sealed-tube charged with **1a** (0.5 g, 3.47 mmol), $K_2S_2O_8$ (1.87 g, 6.94 mmol), $Pd(OAc)_2$ (0.04 g, 0.017 mmol), TFA (4.5 mL) and TFAA (0.5 mL) was heated at 90 ^{o}C for 12 h. After completion as monitored by the TLC, the reaction mixture was evaporated to obtain a residue which was dissolved in EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ solution (50 mL). The mixture was partitioned in a separating funnel, the organic layer separated and the aqueous layer was further extracted with EtOAc (2 x 25 mL). The organic extracts were pooled, dried over anhyd. Na_2SO_4 and evaporated in vacuum to afford the crude product which was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford the pure **3a** (0.34 g, 68%) as a white solid.

2,2'-Di(1*H*-pyrazol-1-yl)biphenyl (3a). Mp 107-109 ^{o}C; R_f = 0.26 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.17 (s, 2H), 7.19-7.26 (m, 4H), 7.32 (t, J = 6.9 Hz, 2H), 7.40-7.44 (m, 2H), 7.48-7.52 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$):106.6, 125.7, 127.9, 128.9, 130.4, 131.2, 133.5, 139.0, 140.5. Mass (ESI+) *m/z* = 287.0. ESI-HRMS calcd. for $C_{18}H_{15}N_4$ (M^++H): 287.1297, found: 287.1293.

1,1'-(3,3'-Dichlorobiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3b). Yield: 83 % (0.51 g from 0.62 g); a white solid; mp 112-114 °C; R_f = 0.30 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.26 (s, 2H), 6.92 (d, J = 7.1 Hz, 2H), 7.12 (t, J = 7.5 Hz, 2H), 7.42 (d, J = 7.7 Hz, 2H), 7.55 (brs, 2H), 7.71 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 106.5, 128.4, 129.3, 130.0, 132.7, 137.1, 138.2, 140.6. Mass (ESI+) *m/z* = 354.8. ESI-HRMS calcd. for $C_{18}H_{13}Cl_2N_4$ (M^++H): 355.0517, found: 355.0522.

1,1'-(3,3'-Dimethylbiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3c). Yield: 80 % (0.44 g from 0.55 g); a white solid; mp 144-146 °C; R_f = 0.38 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 6H), 6.20 (t, J = 2.0 Hz, 2H), 6.84 (d, J = 7.6 Hz, 2H), 7.08 (t, J = 7.6 Hz, 2H), 7.16 (d, J = 7.5 Hz, 2H), 7.53-7.59 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 17.8, 105.8, 127.7, 128.0, 130.1, 136.2, 136.8, 138.5, 139.8. Mass (ESI+) *m/z* = 315.0. ESI-HRMS calcd. for $C_{20}H_{19}N_4$(M^++H): 315.1610, found: 315.1612.

1,1'-(3,3'-Bis(trifluoromethyl)biphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3d). Yield: 74 % (0.54 g from 0.74 g); a white solid; mp 147-149 °C; R_f = 0.20 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.14 (s, 2H), 7.15-7.19 (m, 2H), 7.26 (t, J = 7.4 Hz, 2H), 7.42 (s, 2H), 7.62-7.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 106.6, 121.6, 124.3, 127.0, 128.6, 133.4, 137.2, 138.1, 140.5. Mass (ESI+) *m/z* = 423.0. ESI-HRMS calcd. for $C_{20}H_{13}F_6N_4$ (M^++H): 423.1044, found: 423.1040.

Diethyl 2,2'-di(1*H*-pyrazol-1-yl)biphenyl-3,3'-dicarboxylate (3e) Yield: 60 % (0.45 g from 0.75 g); a brown oil; R_f = 0.30 (hexanes: EtOAc, 80:20, v/v). IR (Neat) ν_{max}: 1717 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, J = 7.1 Hz, 6H), 4.01-4.06 (m, 4H), 6.14 (t, J = 2.1 Hz, 2H), 7.08 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 2H), 7.22 (t, J = 7.7 Hz, 2H), 7.44 (d, J = 1.1 Hz, 2H), 7.51 (d, J = 2.0 Hz, 2H), 7.74 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 61.7, 106.5, 128.2, 130.5, 130.6, 132.5, 133.4, 136.3, 138.2, 140.3, 166.1. Mass (ESI+) *m/z* = 431.1. ESI-HRMS calcd. for $C_{24}H_{23}N_4O_4$ (M^++H): 431.1719, found: 431.1716.

1,1'-(4,4'-Difluorobiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3f). Yield: 45 % (0.25 g from 0.56 g); a yellow solid; mp 120-122 °C; R_f = 0.32 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.14 (t, J = 2.1 Hz, 2H), 6.97 (td, J_1 = 8.4 Hz, J_2 = 2.6 Hz, 2H), 7.06-7.09 (m, 2H), 7.15 (d, J = 2.3 Hz,

2H), 7.18-7.21 (m, 2H), 7.42 (d, J = 1.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 107.2, 113.1 (d, J = 25.2 Hz), 115.1 (d, J = 21.1 Hz), 128.5, 130.2, 132.6 (d, J = 8.6 Hz), 140.2 (d, J = 10.0 Hz), 141.0, 162.5 (d, J = 247.8 Hz,). Mass (ESI+) *m/z* = 323.0. ESI-HRMS calcd. for $C_{18}H_{13}F_2N_4$ (M^++H): 323.1108, found: 323.1105.

1,1'-(4,4'-Dichlorobiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3g). Yield: 48 % (0.30 g from 0.62 g); a yellow oil; R_f = 0.31 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (t, J = 2.1 Hz, 2H), 7.01 (d, J = 8.3 Hz, 2H), 7.18-7.19 (m, 2H), 7.23 (dd, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 2H), 7.44 (d, J = 2.1 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 107.3, 125.9, 130.3, 131.0, 132.1, 134.9, 139.6, 141.0. Mass (ESI+) *m/z* = 354.9. ESI-HRMS calcd. for $C_{18}H_{13}Cl_2N_4$ (M^++H): 355.0517, found: 355.0513.

1,1'-(5,5'-Difluorobiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3h). Yield: 78 % (0.44 g from 0.56 g); an off white solid; mp 144-146 ^{o}C; R_f = 0.22 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (t, J = 2.2 Hz, 2H), 6.79 (dd, J_1 = 8.7 Hz, J_2 = 2.8 Hz, 2H), 7.02-7.07 (m, 2H), 7.23 (d, J = 2.4 Hz, 2H), 7.38 (dd, J_1 = 8.8 Hz, J_2 = 5.2 Hz, 2H), 7.42 (d, J = 1.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 106.9, 116.2 (d, J = 22.3 Hz), 117.4 (d, J = 23.4 Hz), 127.7 (d, J = 8.8 Hz), 130.6, 134.8 (d, J = 5.7 Hz), 135.3, 140.8, 161.6 (d, J = 247.7 Hz). Mass (ESI+) *m/z* = 323.0. ESI-HRMS calcd. for $C_{18}H_{13}F_2N_4$ (M^++H): 323.1108, found: 323.1104.

1,1'-(5,5'-Dichlorobiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3i). Yield: 75 % (0.46 g from 0.62 g); a white solid; mp 160-162 ^{o}C; R_f = 0.22 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (brs, 2H), 7.23-7.26 (m, 4H), 7.41 (brs, 4H), 7.48 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 107.3, 127.0, 129.6, 130.2, 130.9, 133.7, 133.9, 137.6, 141.1. Mass (ESI+) *m/z* = 354.9. ESI-HRMS calcd. for $C_{18}H_{13}Cl_2N_4$ (M^++H): 355.0517, found: 355.0520.

1,1'-(5,5'-Dibromobiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3j). Yield: 70 % (0.54 g from 0.77 g); a white solid; mp 112-114 ^{o}C; R_f = 0.30 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (s, 2H), 7.18-7.26 (m, 3H), 7.34-7.40 (m, 3H), 7.48 (s, 2H), 7.56 (d, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 107.3, 121.4, 127.1, 130.1, 132.5, 133.8, 133.9, 138.0, 141.0. Mass (ESI+) *m/z* = 442.9. ESI-HRMS calcd. for $C_{18}H_{13}Br_2N_4$ (M^++H): 442.9507, found: 442.9510.

1,1'-(5,5'-Dimethylbiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3k). Yield: 72 % (0.39 g from 0.55 g); an off white solid; mp 94-96 ^{o}C; R_f = 0.28 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 6H), 6.08 (t, J = 2.1 Hz, 2H), 6.98 (d, J = 1.2 Hz, 2H), 7.06 (d, J = 2.3 Hz, 2H), 7.13 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.1, 106.3, 125.5, 129.5, 130.3, 131.6, 133.2, 136.7, 137.8, 140.1. Mass (ESI+) *m/z* = 315.0. ESI-HRMS calcd. for $C_{20}H_{19}N_4$ (M^++H): 315.1610, found: 315.1610.

1,1'-(5,5'-Bis(trifluoromethyl)biphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3m). Yield: 74 % (0.55 g from 0.74 g); an off white solid; mp 83-85 ^{o}C; R_f = 0.40 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.17-6.18 (m, 2H), 7.20 (d, J = 2.16 Hz, 2H), 7.38 (d, J = 0.8 Hz, 2H), 7.43 (d, J = 1.3 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.60 (dd, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 107.7, 123.6 (q, J = 272.6 Hz), 126.1, 126.5 (q, J = 3.6 Hz), 128.3 (q, J = 3.7 Hz), 130.1, 130.2 (q, J = 33.2 Hz), 132.9, 141.5, 141.6. Mass (ESI+) *m/z* = 423.0. ESI-HRMS calcd. for $C_{20}H_{13}F_6N_4$ (M^++H): 423.1044, found: 423.1044.

Diethyl 6,6'-di(1*H*-pyrazol-1-yl)biphenyl-3,3'-dicarboxylate (3n) Yield: 72 % (0.54 g from 0.75 g); an off white solid; mp 99-101 ^{o}C; R_f = 0.16 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1716 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.1 Hz, 6H), 4.33 (q, J = 7.1 Hz, 4H), 6.10 (t, J = 1.9 Hz, 2H), 7.02 (d, J = 2.4 Hz, 2H), 7.39 (d, J = 1.2 Hz, 2H), 7.50 (d, J = 1.7 Hz, 2H), 8.00 (d, J = 1.9 Hz, 2H), 8.07 (dd, J_1 = 8.5 Hz, J_2 = 1.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.6, 107.5, 125.2, 129.9, 130.0, 130.7, 132.2, 133.0, 141.2, 142.1, 165.6. Mass (ESI+) *m/z* = 431.1. ESI-HRMS calcd. for $C_{24}H_{23}N_4O_4$ (M^++H): 431.1719, found: 431.1724.

1,1'-(3,3',5,5'-Tetramethylbiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3o). Yield: 74 % (0.44 g from 0.6 g); a white solid; mp 127-128 ^{o}C; R_f = 0.55 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (s, 6H), 2.09 (s, 6H), 6.12 (t, J = 2.1 Hz, 2H), 6.57 (s, 2H), 6.88 (s, 2H), 7.44-7.46 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 17.7, 21.0, 105.6, 128.3, 130.7, 132.2, 135.7, 135.9, 136.5, 137.8, 139.6. Mass (ESI+) *m/z* = 343.1. ESI-HRMS calcd. for $C_{22}H_{23}N_4$ (M^++H): 343.1923, found: 343.1925.

1,1'-(4,4',5,5'-Tetramethylbiphenyl-2,2'-diyl)bis(1*H*-pyrazole) (3p). Yield: 70 % (0.42 g from 0.6 g); a white solid; mp 132-134 ^{o}C; R_f = 0.25 (hexanes: EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 6H), 2.21 (s, 6H), 6.06 (t, J = 2.2 Hz, 2H), 6.93 (s, 2H), 7.09 (d, J = 6.6 Hz, 2H), 7.18-7.20 (m, 2H), 7.38 (d, J = 1.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 19.6, 19.7, 106.4, 126.7, 130.3, 132.4, 136.5, 136.8, 137.6, 140.1. Mass (ESI+) *m/z* = 343.1. ESI-HRMS calcd. for $C_{22}H_{23}N_4$ (M^++H): 343.1923, found: 343.1928.

General procedure for oxidative *ortho*-hydroxylation in *N*-aryl pyrazoles 1a, 1b, 1e and 1j for the synthesis of 2b, 2e and 22a-b as exemplified for the synthesis of 2b.

A 50 mL sealed-tube charged with **1b** (0.12 g, 0.69 mmol), $K_2S_2O_8$ (0.375 g, 1.38 mmol), $Pd(OAc)_2$ (0.008 g, 0.034 mmol), TFA (9.0 mL) and TFAA (1.0 mL) was heated at 90 ^{o}C for 12 h. Following similar experimental procedure as reported for **3a**, a crude product was obtained which was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford the pure **2b** (0.087 g, 67 %) as a brown oil and **3b** (0.003 g, 3%) as a white solid.

3-Chloro-2-(1*H*-pyrazol-1-yl)phenol (2b). R_f = 0.22 (hexanes: EtOAc, 80:20, v/v). IR (Neat) ν_{max} 3368 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (s, 1H), 7.03 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 6.9 Hz, 1H), 7.81 (d, J = 1.2 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 9.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 106.9, 117.1, 122.1, 124.8, 126.5, 129.1, 133.2, 141.1, 152.5. Mass (ESI+) *m/z* = 194.8. ESI-HRMS calcd. for $C_9H_8ClN_2O$ (M^++H): 195.0325, found: 195.0330.

Ethyl 3-hydroxy-2-(1*H*-pyrazol-1-yl)benzoate (2e) Yield: 64 % (0.103 g from 0.15 g); a pale yellow solid; mp 125-127 ^{o}C; R_f = 0.18 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1718 (CO_2Et), 3390 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.1 Hz, 3H), 4.14 (q, J = 7.1 Hz, 2H), 6.42 (m, 1H), 7.15-7.18 (m, 1H), 7.21-7.29 (m, 2H), 7.50 (d, J = 2.2 Hz, 1H), 7.75 (d, J = 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 61.7, 107.1, 121.4, 122.0, 125.1, 126.8, 132.6, 141.2, 151.6, 166.8. Mass (ESI+) *m/z* = 232.9. ESI-HRMS calcd. for $C_{12}H_{13}N_2O_3$ (M^++H): 233.0926, found: 233.0925.**2-(1*H*-Pyrazol-1-yl)benzene-1,3-diol (22a).** Yield: 60 % (0.073 g from 0.1 g); a brown oil; R_f = 0.22 (hexanes: EtOAc, 80:20, v/v). IR (Neat) ν_{max} 3399 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (t, J = 2.2 Hz, 1H),

6.57 (d, J = 8.2 Hz, 2H), 7.01 (t, J = 8.2 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 8.19 (brs, 2H), 8.36 (d, J = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 106.1, 109.4, 127.7, 132.8, 138.6, 149.6. Mass (ESI+) *m/z* = 176.8. ESI-HRMS calcd. for $C_9H_9N_2O_2$ (M^++H): 177.0664, found: 177.0665.

5-Bromo-2-(1*H*-pyrazol-1-yl)benzene-1,3-diol (22b). Yield: 62 % (0.109 g from 0.154 g); a brown oil; R_f = 0.22 (hexanes: EtOAc, 80:20, v/v). IR (Neat) ν_{max} 3399 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (s, 1H), 6.77 (s, 2H), 7.75 (s, 1H), 8.38 (s, 1H), 8.97 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 106.3, 112.7, 114.5, 119.8, 132.8, 138.6, 150.2. Mass (ESI+) *m/z* = 254.8. ESI-HRMS calcd. for $C_9H_8BrN_2O_2$ (M^++H): 254.9769, found: 254.9765.

The syntheses of starting 5-substitutedphenyl-1-phenyl-1*H*-pyrazole-3-carboxylates or 5-phenyl-1-substitutedphenyl-1*H*-pyrazole-3-carboxylates were carried out via the reported methods.

Ethyl 1,5-diphenyl-1*H*-pyrazole-3-carboxylate (5a).[29]

Ethyl 5-(2-chlorophenyl)-1-phenyl-1*H*-pyrazole-3-carboxylate (5b). Yield: 85 % (1.1 g from 1.0 g); a white solid; mp 65-67 ^{o}C; R_f= 0.47 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1722 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.1 Hz, 3H), 4.46 (q, J = 7.1 Hz, 2H), 7.05 (s, 1H), 7.23-7.24 (m, 2H), 7.28 (brs, 4H), 7.30-7.34 (m, 2H), 7.38-7.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.6, 61.3, 111.9, 124.8, 127.0, 128.3, 129.0, 129.4, 130.2, 130.8, 132.2, 139.6, 142.5, 144.3, 162.5. Mass (ESI+) *m/z* = 327.1. ESI-HRMS calcd. for $C_{18}H_{16}ClN_2O_2$ (M^++H): 327.0900, found: 327.0897.

Ethyl 5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-3-carboxylate (5c). Yield: 90 % (1.2 g from 1.0 g); a white solid; mp 113-115 ^{o}C; R_f= 0.46 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1721 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, 3H), 4.46 (q, J = 7.1 Hz, 2H), 6.98-7.03 (m, 3H), 7.17-7.21 (m, 2H), 7.29-7.33 (m, 2H), 7.35-7.37 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.6, 61.3, 110.0, 115.9 (d, J = 21.7 Hz), 125.9, 128.6, 129.2, 130.8 (d, J = 8.2 Hz), 139.5, 143.8, 144.5, 162.5, 162.9 (d, J = 248.1 Hz). Mass (ESI+) *m/z* = 311.2. ESI-HRMS calcd. for $C_{18}H_{16}FN_2O_2$ (M^++H): 311.1196, found: 311.1191.

Ethyl 5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-3-carboxylate (5d).[30]

Ethyl 1-phenyl-5-p-tolyl-1*H*-pyrazole-3-carboxylate (5e). Yield: 88 % (1.1 g from 1.0 g); a white solid; mp 84-86 ^{o}C; R_f = 0.5 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1721 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.2 Hz, 3H), 2.34 (s, 3H), 4.45 (q, J = 7.0 Hz, 2H), 7.01 (s, 1H), 7.34 (m, 5H) . ^{13}C NMR (100 MHz, $CDCl_3$): 14.6, 21.4, 61.2, 109.8, 125.9, 126.8, 138.9, 139.8, 144.4, 144.9, 162.7. Mass (ESI+) *m/z* = 307.2. ESI-HRMS calcd. for $C_{19}H_{19}N_2O_2$ (M^++H): 307.1447, found: 307.1449.

Ethyl 5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-3-carboxylate (5f).[31]

Ethyl 5-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-3-carboxylate (5g). Yield: 80 % (1.0 g from 1.0 g); a white solid; mp 128-130 ^{o}C; R_f = 0.2 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1721 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, J = 7.1 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 7.10 (s, 1H), 7.23-7.26 (m, 2H), 7.30-7.35 (m, 5H), 8.09 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.5, 111.1, 124.0, 126.0, 129.2, 129.6, 135.8, 139.1, 142.4, 144.9, 147.8, 162.1. Mass (ESI+) *m/z* = 338.2. ESI-HRMS calcd. for $C_{18}H_{16}N_3O_4$ (M^++H): 338.1141, found: 338.1145.

Ethyl 5-(2,4-dimethylphenyl)-1-phenyl-1*H*-pyrazole-3-carboxylate (5h). Yield: 72 % (0.375 g from 0.5 g); a brown oil; R_f = 0.56 (hexanes: EtOAc, 80:20, v/v). IR (Neat) ν_{max} 1721 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.1 Hz, 3H), 1.96 (s, 3H), 2.32 (s, 3H), 4.46 (q, J = 7.1 Hz, 2H), 6.91 (s, 1H), 697-6.99 (m, 2H), 7.05-7.07 (m, 1H), 7.24-7.28 (m, 5H) . ^{13}C NMR (100 MHz, $CDCl_3$): 14.6, 19.9, 21.3, 61.2, 111.1, 124.5, 126.8, 127.9, 128.9, 130.6, 131.3, 137.0, 139.4, 139.8, 144.1, 144.2, 162.7. Mass (ESI+) *m/z* = 321.2. ESI-HRMS calcd. for $C_{20}H_{21}N_2O_2$ (M^++H): 321.1603, found: 321.1601.

Ethyl 1-phenyl-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole-3-carboxylate (5i). Yield: 88 % (1.1 g from 1.0 g); a white solid; mp 147-149 ^{o}C; R_f = 0.28 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1717 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.1 Hz, 3H), 3.64 (s, 6H), 3.85 (s, 3H), 4.46 (q, J = 7.1 Hz, 2H), 6.39 (s, 2H), 7.35-7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 56.1, 61.0, 61.3, 106.2, 109.4, 124.7, 126.1, 128.6, 129.1, 138.5, 139.8, 144.4, 144.7, 153.3, 162.5. Mass (ESI+) *m/z* = 383.2. ESI-HRMS calcd. for $C_{21}H_{23}N_2O_5$ (M^++H): 383.1607, found: 383.1602.

Ethyl 1-(2-chlorophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (5j).[32]

Ethyl 1-(3-chlorophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (5k).[33]

Ethyl 1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (5l).[34]

Ethyl 1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (5m).[34]

Ethyl 1-(4-bromophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (5n).[34]

Ethyl 1-(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (5o). Yield: 88 % (1.3 g from 1.0 g); an off white solid; mp 98-100 ^{o}C; R_f = 0.53 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1721 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, 3H), 1.82 (s, 3H), 2.32 (s, 3H), 4.45 (q, J = 7.1 Hz, 2H), 7.05-7.12 (m, 3H), 7.17-7.20 (m, 3H), 7.23-7.26 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.6, 17.1, 20.9, 61.2, 108.4, 127.9, 128.6, 128.7, 129.5, 130.4, 130.8, 132.1, 136.7, 138.9, 144.3, 145.7, 162.7. Mass (ESI+) *m/z* = 321.2. ESI-HRMS calcd. for $C_{20}H_{21}N_2O_2$ (M^++H): 321.1603, found: 321.1607.

Ethyl 1-(3,4-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (5p).[35]

The ethyl 5-(alkyl)-1-(substitutedphenyl)-1*H*-pyrazole-3-carboxylates were prepared according to the literature procedure.[35]

Ethyl 5-methyl-1-phenyl-1*H*-pyrazole-3-carboxylate (8a).[36]

Ethyl 1-(3-chlorophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (8b).[37]

Ethyl 1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (8c).[38]

Ethyl 1-(4-bromophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (8d).[36]

Ethyl 5-methyl-1-p-tolyl-1*H*-pyrazole-3-carboxylate (8e).[36]

Ethyl 1-phenyl-5-propyl-1*H*-pyrazole-3-carboxylate (8f).[39]

Ethyl 5-isopropyl-1-phenyl-1*H*-pyrazole-3-carboxylate (8g). Yield: 85 % (1.2 g from 1.5 g); a brown oil; R_f = 0.56 (hexanes: EtOAc, 80:20, v/v). IR (Neat) ν_{max} 1721 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, J = 6.9 Hz, 6H), 1.32 (t, J = 7.1 Hz, 3H), 2.88-2.97 (m, 1H), 4.34 (q, J = 7.1 Hz, 6H), 6.69 (d, J = 0.4 Hz, 1H), 7.34-7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.6, 22.9, 25.7,

61.1, 105.7, 126.5, 129.1, 129.3, 139.5, 144.0, 152.3, 162.9. Mass (ESI+) *m/z* = 259.2. ESI-HRMS calcd. for $C_{15}H_{19}N_2O_2$ (M^++H): 259.1447, found: 259.1450.

Ethyl 1-phenyl-1*H*-pyrazole-3-carboxylate (8h).[40]

Ethyl 1-phenyl-1*H*-pyrazole-5-carboxylate (11a).[41]

Ethyl 1-(4-bromophenyl)-1*H*-pyrazole-5-carboxylate (11b).[42]

Ethyl 1,3-diphenyl-1*H*-pyrazole-5-carboxylate (11c).[29]

The ethyl 5-methyl-1-(substitutedphenyl)-1*H*-pyrazole-4-carboxylates were prepared according to the literature procedure.[36]

Ethyl 5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (14a).[43]

Ethyl 1-(4-bromophenyl)-5-methyl-1*H*-pyrazole-4-carboxylate (14b).[36]

Ethyl 5-methyl-1-*o*-tolyl-1*H*-pyrazole-4-carboxylate (14c). Yield: 86 % (1.3 g from 1.0 g); a brown oil; R_f = 0.5 (hexanes: EtOAc, 80:20, v/v). IR (Neat) ν_{max} 1721 (CO_2Et) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.2 Hz, 3H), 1.96 (s, 3H), 2.27 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 7.13 (dd, J_1 = 6.9 Hz, J_2 = 0.7 Hz, 1H), 7.22-7.28 (m, 2H), 7.32 (td, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.97 (s, 1H) . ^{13}C NMR (100 MHz, $CDCl_3$): 11.3, 14.6, 17.3, 60.1, 112.1, 126.9, 127.7, 129.9, 131.3, 136.1, 137.8, 141.8, 144.5, 164.0. Mass (ESI+) *m/z* = 245.3. ESI-HRMS calcd. for $C_{14}H_{17}N_2O_2$ (M^++H): 245.1290, found: 245.1295.

Ethyl 1-(2,4-dichlorophenyl)-5-methyl-1*H*-pyrazole-4-carboxylate (14d).[36]

3-Methyl-1,5-diphenyl-1*H*-pyrazole (17).[44]

3-Methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (21).[45]

General procedure for oxidative C(sp2)-H functionalization in substituted *N*-aryl pyrazoles 5a-p, 8a-h, 11a-c, 14a-d, 17 esters as exemplified for 5a.

To a 50 mL sealed-tube were added **5a** (0.5 g, 1.7 mmol), $K_2S_2O_8$ (0.925 g, 3.42 mmol), $Pd(OAc)_2$ (0.019 g, 0.08 mmol), TFA (4.5 mL) and TFAA (0.5 mL) and the mixture was heated at 90 ^oC for 12 h. Similar expertimental procedure as described for **3a** afforded the crude product which was purified by

column chromatography (silica gel, 20% EtOAc in hexanes) to obtain pure **6a** (0.4 g, 76%) as a white solid and **7a** (0.015 g, 3%) also as a white solid.

Ethyl 1-(2-hydroxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (6a). Mp 145-147 ^{o}C; R_f = 0.41 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1721 (CO_2Et), 3423 (OH) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.32 (t, J = 7.0 Hz, 3H), 4.32 (q, J = 7.0 Hz, 2H), 6.89-6.95 (m, 2H), 7.10 (s, 1H), 7.30-7.35 (m, 7H), 9.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 60.3, 107.8, 116.6, 119.1, 127.1, 127.4, 128.3, 128.4, 128.8, 129.3, 130.8, 143.1, 145.6, 152.7, 161.7. Mass (ESI+) *m/z* = 309.0. ESI-HRMS calcd. for $C_{18}H_{17}N_2O_3$ (M^++H): 309.1239, found: 309.1242.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-phenyl-1*H*-pyrazole-3-carboxylate) (7a). Mp 137-139 ^{o}C; R_f = 0.27 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1728 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.1 Hz, 6H), 4.38-4.39 (m, 4H), 6.09-6.10 (m, 2H), 6.55 (d, J = 7.4 Hz, 4H), 6.74 (s, 2H), 6.89 (s, 2H), 7.00 (t, J = 7.4 Hz, 4H), 7.14 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 6.4 Hz, 2H), 7.43-7.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 60.7, 109.8, 127.7, 127.8, 128.0, 128.3, 128.5, 128.8, 130.0, 131.8, 134.1, 137.0, 144.4, 144.8, 162.1. Mass (ESI+) *m/z* = 583.2. ESI-HRMS calcd. for $C_{36}H_{31}N_4O_4$ (M^++H): 583.2345, found: 583.2340.

Ethyl 5-(2-chlorophenyl)-1-(2-hydroxyphenyl)-1*H*-pyrazole-3-carboxylate (6b). Yield: 45 % (0.25 g from 0.55 g); a white solid; mp 112-114 ^{o}C; R_f = 0.62 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1719 (CO_2Et), 3428 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 6.7 Hz, 3H), 4.44-4.58 (m, 2H), 6.59-6.62 (m, 2H), 7.08-7.16 (m, 3H), 7.26-7.30 (m, 2H), 7.38-7.43 (m, 2H), 8.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.6, 112.0, 118.8, 119.6, 123.7, 125.6, 127.2, 129.0, 129.6, 130.4, 131.1, 132.0, 134.2, 142.4, 144.0, 150.5, 161.7. Mass (ESI+) *m/z* = 342.9. ESI-HRMS calcd. for $C_{18}H_{16}ClN_2O_3$ (M^++H): 343.0849, found: 343.0854.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-(2-chlorophenyl)-1*H*-pyrazole-3-carboxylate) (7b). Yield: 29 % (0.16 g from 0.55 g); a white solid; mp 210-212 ^{o}C; R_f = 0.37 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1724 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, J = 6.3 Hz, 6H), 4.37-4.39 (m, 4H), 6.24 (brs, 2H), 6.41 (d, J = 6.8 Hz, 2H), 6.83-6.85 (m, 4H), 7.00 (s, 2H), 7.09-7.10 (m, 4H), 7.31-

7.41 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 60.8, 112.1, 126.6, 128.7, 128.9, 129.1, 129.3, 129.5, 129.7, 131.4, 131.8, 133.2, 133.8, 137.7, 141.7, 144.6, 162.1. Mass (ESI+) *m/z* = 651.1. ESI-HRMS calcd. for $C_{36}H_{29}Cl_2N_4O_4$ (M^++H): 651.1566, found: 651.1562.

Ethyl 5-(4-fluorophenyl)-1-(2-hydroxyphenyl)-1*H*-pyrazole-3-carboxylate (6c). Yield: 70 % (0.39 g from 0.53 g); a white solid; mp 132-134 ^{o}C; R_f = 0.60 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1721 (CO_2Et), 3399 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 6.0 Hz, 3H), 4.44 (q, *J* = 6.6 Hz, 2H), 6.68-6.74 (m, 2H), 7.02-7.06 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.20-7.26 (m, 3H), 8.41 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 61.5, 110.1, 116.1 (d, *J* = 21.9 Hz), 118.9, 119.9, 125.5 (d, *J* = 3.3 Hz), 125.6, 125.9, 130.0, 130.8 (d, *J* = 8.3 Hz), 144.4, 144.7, 151.1, 161.9, 163.3 (d, *J* = 249.7 Hz). Mass (ESI+) *m/z* = 327.0. ESI-HRMS calcd. for $C_{18}H_{16}FN_2O_3$ (M^++H): 327.1145, found: 327.1142.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-(4-fluorophenyl)-1*H*-pyrazole-3-carboxylate) (7c). Yield: 12 % (0.06 g from 0.53 g); a white solid; mp 112-114 ^{o}C; R_f = 0.10 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1727 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 6.7 Hz, 6H), 4.39 (brs, 4H), 6.15 (brs, 2H), 6.52 (brs, 4H), 6.71-6.77 (m, 6H), 6.99 (brs, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.46 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.5, 110.3, 116.1 (d, *J* = 21.8 Hz), 118.9, 119.9, 125.5 (d, *J* = 3.2 Hz), 125.5, 125.6, 130.0, 130.9 (d, *J* = 8.3 Hz), 144.5, 144.6, 150.9, 161.8, 163.4 (d, *J* = 250.4 Hz). Mass (ESI+) *m/z* = 619.2. ESI-HRMS calcd. for $C_{36}H_{29}F_2N_4O_4$ (M^++H): 619.2157, found: 619.2162.

Ethyl 5-(4-chlorophenyl)-1-(2-hydroxyphenyl)-1*H*-pyrazole-3-carboxylate (6d). Yield: 44 % (0.26 g from 0.55 g); a white solid; mp 143-145 ^{o}C; R_f = 0.44 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1722 (CO_2Et), 3403 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.1 Hz, 3H), 4.44 (d, *J* = 7.1 Hz, 2H), 6.69-6.76 (m, 2H), 7.05 (s, 1H), 7.13-7.16 (m, 1H), 7.19-7.23 (m, 2H), 7.25-7.26 (m, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.6, 110.4, 119.0, 120.0, 125.4, 125.7, 127.8, 129.3, 130.1, 135.6, 144.4, 144.6, 150.9, 161.7. Mass (ESI+) *m/z* = 343.1. ESI-HRMS calcd. for $C_{18}H_{16}ClN_2O_3$ (M^++H): 343.0849, found: 343.0846.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylate) (7d). Yield: 28 % (0.15 g from 0.55 g); a white solid; mp 162-164 ^{o}C; R_f = 0.41 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1722 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.1 Hz, 6H), 4.39 (brs, 4H), 6.1 (s, 1H), 6.48 (d, J = 7.8 Hz, 4H), 6.73 (s, 2H), 6.99 (d, J = 6.4 Hz, 6H), 7.26 (s, 1H), 7.32 (t, J = 7.4 Hz, 2H), 7.45 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 60.9, 110.0, 128.2, 128.4, 128.6, 128.9, 129.1, 131.9, 133.7, 134.1, 136.7, 143.2, 145.0, 162.0. Mass (ESI+) *m/z* = 650.9. ESI-HRMS calcd. for $C_{36}H_{29}Cl_2N_4O_4$ (M^++H): 651.1566, found: 651.1562.

Ethyl 1-(2-hydroxyphenyl)-5-p-tolyl-1*H*-pyrazole-3-carboxylate (6e). Yield: 74 % (0.41 g from 0.52 g); a white solid; mp 156-157 ^{o}C; R_f = 0.53 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1726 (CO_2Et), 3400 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 6.7 Hz, 3H), 2.36 (s, 3H), 4.44 (q, J = 6.9 Hz, 2H,), 6.67 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 7.02 (s, 1H), 7.13-7.15 (m, 5H), 7.20 (t, J = 7.2 Hz, 1H), 8.53 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 21.4, 61.4, 110.2, 118.8, 119.7, 125.4, 125.5, 126.4, 128.8, 129.6, 139.5, 144.3, 145.7, 150.8, 161.8. Mass (ESI+) *m/z* = 323.0 ESI-HRMS calcd. for $C_{19}H_{19}N_2O_3$ (M^++H): 323.1396, found: 323.1391.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-p-tolyl-1*H*-pyrazole-3-carboxylate) (7e). Yield: 8 % (0.04 g from 0.52 g); a yellow solid; mp 223-225 ^{o}C; R_f = 0.16 (hexanes: EtOAc, 60:40, v/v). IR (KBr) ν_{max}: 1727 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (t, J = 6.7 Hz, 6H), 2.20 (s, 6H), 4.37 (brs, 4H), 6.44 (d, J = 5.0 Hz, 4H), 6.71 (s, 2H), 6.82 (d, J = 6.1 Hz, 4H), 6.91 (brs, 2H), 7.25-7.28 (m, 4H), 7.39 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 21.3, 60.6, 109.4, 127.0, 127.6, 128.0, 128.4, 128.6, 128.9, 132.0, 134.2, 137.1, 137.7, 144.6, 144.7, 162.2. Mass (ESI+) *m/z* = 611.4. ESI-HRMS calcd. for $C_{38}H_{35}N_4O_4$ (M^++H): 611.2658, found: 611.2657.

Ethyl 1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (6f). Yield: 40 % (0.23g from 0.55 g); a yellow solid; mp 115-117 ^{o}C; R_f = 0.20 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1724 (CO_2Et), 3409 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.1 Hz, 3H), 3.82 (s, 3H), 4.43 (q, J = 7.1 Hz, 2H), 6.66-6.67 (m, 1H), 6.78 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 6.86 (dd, J_1 = 8.8 Hz, J_2 = 1.9 Hz, 2H), 6.99 (s, 1H), 7.13 (dd, J_1 = 8.2 Hz, J_2 = 1.3 Hz, 1H), 7.17-7.22 (m, 3H), 8.53

(brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 55.5, 61.4, 110.0, 114.4, 118.9, 119.7, 121.6, 125.4, 125.6, 129.6, 130.3, 144.4, 145.5, 150.9, 160.4, 161.9. Mass (ESI+) *m/z* = 339.0 ESI-HRMS calcd. for $C_{19}H_{19}N_2O_4$ (M^++H): 339.1345, found: 339.1340.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate) (7f). Yield: 32 % (0.18 g from 0.55 g); an off white solid; mp 165-168 ^{o}C; R_f = 0.08 (hexanes: EtOAc, 60:40, v/v). IR (KBr) ν_{max}: 1725 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.0 Hz, 6H), 3.68 (s, 6H), 4.30 (d, J = 5.0 Hz, 4H), 6.14-6.22 (m, 2H), 6.40-6.49 (m, 8H), 6.61 (s, 2H), 6.89 (s, 2H), 7.19-7.22 (m, 2H), 7.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6): 14.2, 55.2, 60.4, 108.9, 113.5, 122.3, 127.8, 128.3, 128.5, 128.8, 131.6, 134.0, 136.8, 144.1, 144.4, 159.2, 162.0. Mass (ESI+) *m/z* = 643.2. ESI-HRMS calcd. for $C_{38}H_{35}N_4O_6$ (M^++H): 643.2557, found: 643.2559.

Ethyl 1-(2-hydroxyphenyl)-5-(4-nitrophenyl)-1*H*-pyrazole-3-carboxylate (6g) Yield: 35 % (0.21 g from 0.58 g); an off white solid; mp 192-194 ^{o}C; R_f = 0.40 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1726 (CO_2Et), 3400 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 5.7 Hz, 3H), 4.45 (q, J = 5.7 Hz, 2H), 6.73-6.74 (m, 2H), 7.15-7.17 (m, 2H), 7.26-7.29 (m, 1H), 7.44-7.46 (m, 2H), 8.01 (s, 1H), 8.21 (dd, J_1 = 5.5 Hz, J_2 = 1.6 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 61.7, 111.2, 119.2, 120.3, 124.1, 125.3, 125.9, 129.6, 130.6, 135.5, 143.2, 144.9, 148.0, 150.9, 161.5. Mass (ESI+) *m/z* = 354.0 ESI-HRMS calcd. for $C_{18}H_{16}N_3O_5$ (M^++H): 354.1090, found: 354.1093.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-(4-nitrophenyl)-1*H*-pyrazole-3-carboxylate) (7g). Yield: 20 % (0.12 g from 0.58 g); a white solid; mp 210-212 ^{o}C; R_f = 0.12 (hexanes: EtOAc, 60:40, v/v). IR (KBr) ν_{max}: 1733 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, 6H), 4.42-4.46 (m, 4H), 6.09 (brs, 2H), 6.72 (d, J = 7.5 Hz, 4H), 6.85 (s, 2H), 6.93 (brs, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7.53 (s, 2H), 7.89 (d, J = 8.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 60.9, 111.0, 123.4, 128.0, 128.3, 129.3, 129.4, 131.6, 133.0, 135.8, 136.4, 141.9, 145.2, 147.0, 161.5. Mass (ESI+) *m/z* = 673.1. ESI-HRMS calcd. for $C_{36}H_{29}N_6O_8$ (M^++H): 673.2047, found: 673.2046.

Ethyl 5-(2,4-dimethylphenyl)-1-(2-hydroxyphenyl)-1*H*-pyrazole-3-carboxylate (6h). Yield: 44 % (0.25 g from 0.55 g); a white solid; mp 107-108 ^{o}C; R_f = 0.40 (hexanes: EtOAc, 80:20, v/v). IR (KBr)

ν_{max}: 1722 (CO_2Et), 3401 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, 3H), 1.91 (s, 3H), 2.35 (s, 3H), 4.44 (q, J = 7.1 Hz, 2H), 6.59 (dt, J_1 = 6.8 Hz, J_2 = 1.7 Hz, 1H), 6.62 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 6.93 (s, 1H), 7.01-7.04 (m, 2H), 7.09-7.12 (m, 2H), 7.13 (d, J = 1.8 Hz, 1H), 9.26 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 19.6, 21.4, 61.5, 111.2, 118.8, 119.5, 123.4, 125.7, 126.4, 127.1, 129.2, 130.4, 131.6, 137.0, 139.9, 143.7, 145.2, 150.3, 161.8. Mass (ESI+) *m/z* = 337.1. ESI-HRMS calcd. for $C_{20}H_{21}N_2O_3$ (M^++H): 337.1552, found: 337.1552.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-(2,4-dimethylphenyl)-1*H*-pyrazole-3-carboxylate) (7h). Yield: 30 % (0.165 g from 0.55 g); a white solid; mp 70-72 ^oC; R_f= 0.24 (hexanes: EtOAc, 60:40, v/v). IR (KBr) ν_{max}: 1735 (CO_2Et) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 6H), 1.63 (s, 6H), 2.14 (s, 6H), 4.30 (q, J = 7.1 Hz, 4H), 5.98 (d, J = 7.8 Hz, 2H,), 6.09 (d, J = 8.0 Hz, 2H), 6.46 (d, J = 8.0 Hz, 2H), 6.60 (s, 2H), 6.64 (s, 2H), 6.86 (t, J = 8.3 Hz, 2H), 7.20-7.24 (m, 2H), 7.32 (d, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 20.5, 21.3, 60.8, 111.0, 126.0, 126.1, 128.5, 128.7, 128.8, 129.7, 131.1, 131.6, 134.3, 137.0, 137.5, 137.9, 143.6, 144.4, 162.5. Mass (ESI+) *m/z* = 639.4. ESI-HRMS calcd. for $C_{40}H_{39}N_4O_4$ (M^++H): 639.2971, found: 639.2973.

Ethyl 1-(2-hydroxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole-3-carboxylate (6i). Yield: 72 % (0.49 g from 0.65 g); an off white solid; mp 150-152 ^oC; R_f= 0.12 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1721 (CO_2Et), 3400 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.1 Hz, 3H), 3.64 (s, 6H), 3.85 (s, 3H), 4.46 (d, J = 7.1 Hz, 2H), 6.39 (s, 2H), 7.04 (s, 1H), 7.37-7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 56.2, 61.1, 61.5, 106.2, 108.5, 109.9, 118.8, 119.9, 124.4, 125.9, 129.9, 138.9, 144.4, 145.5, 150.9, 153.4, 161.9. Mass (ESI+) *m/z* = 399.5. ESI-HRMS calcd. for $C_{21}H_{23}N_2O_6$ (M^++H): 399.1556, found: 399.1553.

Ethyl 1-(5-chloro-2-hydroxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (6k). Yield: 78 % (0.46 g from 0.55 g); a white solid; mp 118-120 ^oC; R_f= 0.36 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1721 (CO_2Et), 3411 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 6.9 Hz, 3H), 4.44 (d, J = 6.9 Hz, 2H), 6.73 (brs, 1H), 7.05-7.08 (m, 2H), 7.16-7.17 (m, 1H), 7.26-7.29 (m, 2H), 7.40-7.42 (m, 3H), 8.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.6, 110.4, 110.3, 120.1, 124.3, 125.5, 126.2,

128.9, 129.1, 129.7, 129.8, 144.6, 146.0, 149.9, 161.7. Mass (ESI+) *m/z* = 342.9. ESI-HRMS calcd. for $C_{18}H_{16}ClN_2O_3$ (M^++H): 343.0849, found: 343.0853.

Diethyl 1,1'-(4,4'-dichlorobiphenyl-2,2'-diyl)bis(5-phenyl-1*H*-pyrazole-3-carboxylate) (7k). Yield: 10 % (0.06 g from 0.55 g); a white solid; mp 230-232 ^oC; R_f= 0.30 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1731 (CO_2Et) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 6.4 Hz, 6H), 4.40 (brs, 4H), 5.90 (brs, 2H), 6.60 (d, *J* = 7.2 Hz, 4H), 6.76 (s, 2H), 6.81 (d, *J* = 7.3 Hz, 2H), 7.70 (t, *J* = 6.7 Hz, 4H), 7.18 (t, *J* = 6.7 Hz, 2H), 7.55 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.9, 61.3, 110.6, 128.0, 128.5, 128.7, 128.9, 129.6, 130.1, 131.8, 132.7, 134.9, 138.1, 144.8, 145.8, 162.3. Mass (ESI+) *m/z* = 651.0. ESI-HRMS calcd. for $C_{36}H_{29}Cl_2N_4O_4$ (M^++H): 651.1566, found: 651.1563.

Ethyl 1-(4-fluoro-2-hydroxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (6l). Yield: 41 % (0.23 g from 0.53 g); a white solid; mp 224-226 ^oC; R_f= 0.51 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1730 (CO_2Et), 3400 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.1 Hz, 3H), 4.44 (q, *J* = 7.1 Hz, 2H), 6.36-6.41 (m, 1H), 6.70 (dd, J_1 = 9.0 Hz, J_2 = 5.8 Hz, 1H), 6.85 (dd, J_1 = 9.8 Hz, J_2 = 2.8 Hz, 1H), 7.05 (s, 1H), 7.25-7.28 (m, 2H), 7.34-7.40 (m, 3H), 8.77 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.6, 106.1 (d, *J* = 25.4 Hz), 106.9 (d, *J* = 23.4 Hz), 110.3, 122.0, 126.5, 126.6 (d, *J* = 10.4 Hz), 128.9 (d, *J* = 11.3 Hz), 129.5, 144.4, 145.7, 152.6 (d, *J* = 12.8 Hz), 161.7, 162.8 (d, *J* = 247.4 Hz). Mass (ESI+) *m/z* = 327.3. ESI-HRMS calcd. for $C_{18}H_{16}FN_2O_3$ (M^++H): 327.1145, found: 327.1141.

Diethyl 1,1'-(5,5'-difluorobiphenyl-2,2'-diyl)bis(5-phenyl-1*H*-pyrazole-3-carboxylate) (7l). Yield: 24 % (0.13 g from 0.53 g); a yellow oil; R_f= 0.16 (hexanes: EtOAc, 60:40, v/v). IR (Neat) ν_{max}: 1733 (CO_2Et) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.1 Hz, 6H), 4.38-4.40 (m, 4H), 5.65 (brs, 2H), 6.58 (d, *J* = 7.4 Hz, 4H), 6.75 (s, 2H), 7.00-7.05 (m, 2H), 7.08 (t, *J* = 7.8 Hz, 4H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.46-7.48 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 60.9, 109.8, 116.2 (d, *J* = 22.4 Hz), 118.0 (d, *J* = 23.7 Hz), 127.6, 128.4 (d, *J* = 12.1 Hz), 129.5, 130.0 (d, *J* = 8.8 Hz), 133.2, 134.8, 144.5, 145.1, 162.0, 162.2 (d, *J* = 250.7 Hz). Mass (ESI+) *m/z* = 619.1. ESI-HRMS calcd. for $C_{36}H_{29}F_2N_4O_4$ (M^++H): 619.2157, found: 619.2152.

Ethyl 1-(4-chloro-2-hydroxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (6m). Yield: 48 % (0.28 g from 0.55 g); a white solid; mp 170-172 ^{o}C; R_f = 0.21 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1722 (CO_2Et), 3400 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3H), 4.37 (d, J = 7.1 Hz, 2H), 6.56-6.57 (m, 2H), 6.97 (s, 1H), 7.08-7.09 (m, 1H), 7.19-7.21 (m, 2H), 7.29-7.35 (m, 3H), 8.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.6, 110.5, 119.2, 120.0, 124.3, 126.2, 128.9, 129.1, 129.6, 134.9, 144.5, 145.7, 151.8, 161.7. Mass (ESI+) *m/z* = 343.3. ESI-HRMS calcd. for $C_{18}H_{16}ClN_2O_3$ (M^++H): 343.0849, found: 343.0851.

Diethyl 1,1'-(5,5'-dichlorobiphenyl-2,2'-diyl)bis(5-phenyl-1*H*-pyrazole-3-carboxylate) (7m). Yield: 22 % (0.12 g from 0.55 g); a white solid; mp 217-219 ^{o}C; R_f = 0.10 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1729 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 6H), 4.33 (brs, 4H), 5.87 (s, 2H), 6.50 (d, J = 7.2 Hz, 4H), 6.68 (s, 2H), 7.03 (t, J = 7.6 Hz, 4H), 7.12-7.18 (m, 2H), 7.21-7.24 (m, 2H), 7.38 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 60.9, 110.0, 127.5, 128.6, 128.7, 129.2, 129.4, 129.5, 131.2, 134.2, 134.8, 135.6, 144.5, 145.3, 162.0. Mass (ESI+) *m/z* = 651.4. ESI-HRMS calcd. for $C_{36}H_{29}Cl_2N_4O_4$ (M^++H): 651.1566, found: 651.1562.

Ethyl 1-(4-bromo-2-hydroxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (6n). Yield: 40 % (0.26 g from 0.63 g); a white solid; mp 122-124 ^{o}C; R_f = 0.30 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1722 (CO_2Et), 3394 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, 3H), 4.44 (d, J = 7.1 Hz, 2H), 6.60 (d, J = 8.6 Hz, 1H), 6.78 (dd, J_1 = 8.6 Hz, J_2 = 2.1 Hz, 1H), 7.04 (s, 1H), 7.26 (s, 1H), 7.27-7.28 (m, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.36-7.41 (m, 3H), 7.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.6, 110.6, 122.3, 122.6, 122.9, 124.7, 126.3, 129.0, 129.1, 129.6, 144.5, 145.7, 151.8, 161.6. Mass (ESI+) *m/z* = 387.0. ESI-HRMS calcd. for $C_{18}H_{16}BrN_2O_3$ (M^++H): 387.0344, found: 387.0349.

Diethyl 1,1'-(5,5'-dibromobiphenyl-2,2'-diyl)bis(5-phenyl-1*H*-pyrazole-3-carboxylate) (7n). Yield: 22 % (0.14 g from 0.63 g); a brown solid; mp 134-136 ^{o}C; R_f = 0.10 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1732 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.1 Hz, 6H), 4.43 (q, J = 7.2 Hz, 4H), 6.09 (s, 1H), 6.56 (d, J = 7.2 Hz, 3H), 6.74 (s, 2H), 7.11 (t, J = 7.6 Hz, 4H), 7.26-

7.32 (m, 4H), 7.36-7.46 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 60.7, 109.9, 122.8, 127.2, 128.6, 128.9, 129.6, 132.3, 133.9, 134.1, 135.9, 144.4, 145.2, 161.8. Mass (ESI+) *m/z* = 738.9. ESI-HRMS calcd. for $C_{36}H_{29}Br_2N_4O_4$ (M^++H): 739.0556, found: 739.0557.

Ethyl 1-(2-hydroxy-4,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (6p). Yield: 38% (0.22 g from 0.55 g); a yellow solid; mp 122-123 ^{o}C; R_f = 0.28 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1720 (CO_2Et), 3400 (OH) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.35 (t, *J* = 7.1 Hz, 3H), 2.16 (s, 3H), 2.22 (s, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 6.73 (s, 1H), 7.01-7.11 (m, 2H), 7.34-7.36 (m, 5H), 9.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 18.7, 19.8, 61.4, 110.0, 119.5, 123.1, 126.2, 127.9, 128.7, 128.9, 129.2, 129.6, 138.6, 144.1, 145.4, 148.4, 162 0. Mass (ESI+) *m/z* = 337.4 ESI-HRMS calcd. for $C_{20}H_{21}N_2O_3$ (M^++H): 337.1552, found: 337.1550.

Diethyl 1,1'-(4,4',5,5'-tetramethylbiphenyl-2,2'-diyl)bis(5-phenyl-1*H*-pyrazole-3-carboxylate) (7p). Yield: 20 % (0.11 g from 0.55 g); a yellow solid; mp 187-189 ^{o}C; R_f = 0.16 (hexanes: EtOAc, 60:40, v/v). IR (KBr) ν_{max}: 1733 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.2 Hz, 6H), 1.83 (s, 6H), 2.15 (s, 6H), 4.34 (q, *J* = 7.1 Hz, 4H), 5.62 (s, 2H), 6.50 (d, *J* = 7.4 Hz, 4H), 6.63 (s, 2H), 6.91 (t, *J* = 7.7 Hz, 4H), 7.05 (t, *J* = 7.4 Hz, 2H), 7.16 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 19.4, 19.6, 60.7, 109.7, 127.5, 127.8, 127.9, 128.3, 130.0, 131.0, 132.7, 134.6, 137.1, 137.4, 144.2, 144.3, 162.2. Mass (ESI+) *m/z* = 639.2. ESI-HRMS calcd. for $C_{40}H_{39}N_4O_4$ (M^++H): 639.2971, found: 639.2968.

Ethyl 1-(2-hydroxyphenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (9a). Yield: 74 % (0.31 g from 0.40 g); a yellow solid; mp 141-142 ^{o}C; R_f = 0.16 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1721 (CO_2Et), 3400 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 6.9 Hz, 3H), 2.35 (s, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 6.71 (s, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 7.16-7.23 (m, 2H), 8.36 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): 12.8, 14.5, 61.3, 109.7, 118.9, 120.0 124.7, 125.7, 130.0, 142.1, 144.0, 151.2, 162 0. Mass (ESI+) *m/z* = 247.4 ESI-HRMS calcd. for $C_{13}H_{15}N_2O_3$ (M^++H): 247.1083, found: 247.1089.

Ethyl 1-(5-chloro-2-hydroxyphenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (9b). Yield: 74 % (0.4 g from 0.45 g); a white solid; mp 131-132 ^{o}C; R_f = 0.20 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1723 (CO_2Et), 3393 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 3H), 2.36 (s, 3H), 4.32 (q, J = 7.1 Hz, 2H), 6.69 (s, 1H), 6.98 (d, J = 9.4 Hz, 1H), 7.16-7.19 (m, 2H), 8.63 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$): 12.7, 14.4, 61.4, 109.2, 120.4, 124.7, 125.3, 126.6, 130.2, 142.6, 144.0, 150.1, 161.7. Mass (ESI+) *m/z* = 281.5 ESI-HRMS calcd. for $C_{13}H_{14}ClN_2O_3$ (M^++H): 281.0693, found: 281.0697.

Ethyl 1-(4-fluoro-2-hydroxyphenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (9c). Yield: 72 % (0.32 g from 0.42 g); a white solid; mp 124-125 ^{o}C; R_f = 0.20 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1716 (CO_2Et), 3400 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 3H), 2.30 (s, 3H), 4.32 (q, J = 7.1 Hz, 2H), 6.60 (dt, J_1 = 8.2 Hz, J_2 = 2.6 Hz 1H), 6.68 (s, 1H), 6.73 (dd, , J_1 = 9.7 Hz, , J_2 = 2.6 Hz, 1H), 7.12 (m, 1H), 8.67 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$): 12.3, 14.4, 61.3, 106.3 (d, J = 25.2 Hz), 107.3 (d, J = 23.2 Hz), 109.1, 122.4, 126.7 (d, J = 10.6 Hz), 142.5, 143.8, 153.1 (d, J = 12.9 Hz), 161.8, 163.3 (d, J = 246.7 Hz). Mass (ESI+) *m/z* = 264.9 ESI-HRMS calcd. for $C_{13}H_{14}FN_2O_3$ (M^++H): 265.0988, found: 265.0983.

Ethyl 1-(4-bromo-2-hydroxyphenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (9d). Yield: 75 % (0.42 g from 0.53 g); a white solid; mp 165-167 ^{o}C; R_f = 0.20 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1720 (CO_2Et), 3391 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 3H), 2.35 (s, 3H), 4.32 (q, J = 7.1 Hz, 2H), 6.68 (d, J = 0.5 Hz, 1H), 7.03 (d, J = 1.0 Hz, 2H), 7.19 (s, 1H), 8.88 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.5, 14.4, 61.4, 109.4, 122.4, 123.2, 123.3 125.1, 126.2, 142.5, 144.0, 152.2, 161.8. Mass (ESI+) *m/z* = 324.9. ESI-HRMS calcd. for $C_{13}H_{14}BrN_2O_3$ (M^++H): 325.0188, found: 325.0184.

Ethyl 1-(2-hydroxy-4-methylphenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (9e). Yield: 73 % (0.32 g from 0.42 g); a white solid; mp 92-94 ^{o}C; R_f = 0.10 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1722 (CO_2Et), 3398 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.0 Hz, 3H), 2.28 (s, 3H), 2.33 (s, 3H), 4.33 (q, J = 7.1 Hz, 2H), 6.68-6.70 (m, 2H), 6.87 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 12.6, 14.5, 21.4, 61.2, 109.4, 119.2, 120.8, 123.4, 124.7, 140.5, 142.1, 143.7, 150.9, 162.1. Mass (ESI+) *m/z* = 260.9. ESI-HRMS calcd. for $C_{14}H_{17}N_2O_3$ (M^++H): 261.1239, found: 261.1235.

Ethyl 1-(2-hydroxyphenyl)-5-propyl-1*H*-pyrazole-3-carboxylate (9f). Yield: 35 % (0.16 g from 0.44 g); a white solid; mp 68-70 ^{o}C; R_f = 0.20 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max}: 1716 (CO_2Et), 3400 (OH) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (t, J = 7.4 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.50-159 (m, 2H), 2.44 (t, J = 7.6 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 6.71 (s, 1H), 6.97(td, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1H), 7.09 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.27 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.39 (td, J_1 = 7.8 Hz, J_2 = 1.7 Hz, 1H), 9.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 14.5, 21.9, 28.4, 61.3, 108.4, 118.7, 120.1, 125.3, 125.9, 130.2, 144.2, 147.1, 151.3, 162.1; Mass (ESI+) *m/z* = 275.0 ESI-HRMS calcd. for $C_{15}H_{19}N_2O_3$ (M^++H): 275.1396, found: 275.1392.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-propyl-1*H*-pyrazole-3-carboxylate) (10f). Yield: 18 % (0.08 g from 0.44 g); a yellow oil; R_f= 0.32 (hexanes: EtOAc, 60:40, v/v). IR (Neat) ν_{max}: 1733 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.4 Hz, 6H), 1.27 (t, J = 7.7 Hz, 6H), 1.45-1.49 (m, 4H), 2.45 (brs, 4H), 4.26 (q, J = 7.2 Hz, 4H), 6.54 (s, 2H), 6.83 (brs, 2H), 7.12-7.16 (m, 2H), 7.26 (d, J = 4.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.6, 14.5, 21.9, 27.6, 60.8, 107.3, 128.4, 128.8, 129.2, 130.4, 135.1, 137.5, 143.7, 147.4, 162.8. Mass (ESI+) *m/z* = 515.3. ESI-HRMS calcd. for $C_{30}H_{35}N_4O_4$ (M^++H): 515.2658, found: 515.2657.

Ethyl 1-(2-hydroxyphenyl)-5-isopropyl-1*H*-pyrazole-3-carboxylate (9g). Yield: 42 % (0.20 g from 0.44 g); a white solid; mp 142-144 ^{o}C; R_f = 0.22 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1720 (CO_2Et), 3399 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (d, J = 6.8 Hz, 6H), 1.31 (t, J = 7.1 Hz, 3H), 2.89-3.00 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 6.69 (s, 1H), 6.85 (td, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 6.96 (dd, J_1 = 7.0 Hz, J_2 = 1.2 Hz, 1H), 7.12-7.19 (m, 2H), 7.79 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 22.7, 25.7, 29.8, 61.2, 105.9, 118.6, 120.2, 126.3, 130.5, 144.3, 151.7, 153.7, 162.3. Mass (ESI+) *m/z* = 275.5. ESI-HRMS calcd. for $C_{15}H_{19}N_2O_3$ (M^++H): 275.1396, found: 275.1391.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-isopropyl-1*H*-pyrazole-3-carboxylate) (10g). Yield: 20 % (0.09 g from 0.44 g); a white solid; mp 128-130 ^{o}C; R_f = 0.10 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1722 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 12H), 1.26 (t, J = 7.1 Hz, 6H), 3.08-3.19 (m, 2H), 4.25 (d, J = 7.1 Hz, 4H), 6.56 (s, 2H), 6.77 (d, J = 7.1 Hz, 2H), 7.12 (td, J_1 = 7.5 Hz, J_2 = 1.3 Hz, 2H), 7.26 (td, J_1 = 7.4 Hz, J_2 = 1.4 Hz, 2H), 7.32-7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 23.0, 25.1, 60.6, 105.1, 128.3, 128.6, 129.1, 129.9, 134.9, 137.5, 143.7, 154.0, 162.7. Mass (ESI+) *m/z* = 515.5. ESI-HRMS calcd. for $C_{30}H_{35}N_4O_4$ (M^++H): 515.2658, found: 515.2662.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(1*H*-pyrazole-3-carboxylate) (10h). Yield: 80 % (0.296 g from 0.370 g); a brown oil; R_f = 0.27 (hexanes: EtOAc, 80:20, v/v). IR (Neat) ν_{max} 1719 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 6H), 4.34 (q, J = 7.1 Hz, 4H), 6.72 (d, J = 2.4 Hz, 2H), 7.21 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 2H), 7.36 (td, J_1 = 7.0 Hz, J_2 = 1.4 Hz, 4H), 7.44 (td, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 2H), 7.53 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 61.0, 109.6, 126.5, 128.9, 129.3, 131.0, 132.1, 133.4, 138.6, 144.9, 162.3. Mass (ESI+) *m/z* = 431.2. ESI-HRMS calcd. for $C_{24}H_{23}N_4O_4$ (M^++H): 431.1719, found: 431.1714.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(1*H*-pyrazole-5-carboxylate) (13a). Yield: 72 % (0.26 g from 0.37 g); an off white solid; mp 87-89 ^{o}C; R_f = 0.47 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1725 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.1 Hz, 6H), 4.14 (q, J = 7.1 Hz, 4H), 6.80 (d, J = 1.8 Hz, 2H), 7.23-7.26 (m, 4H), 7.33-7.36 (m, 4H), 7.46 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 61.3, 112.0, 128.1, 128.3, 128.7, 131.9, 134.8, 135.2, 138.4, 139.4, 159.1. Mass (ESI+) *m/z* = 431.2. ESI-HRMS calcd. for $C_{24}H_{23}N_4O_4$ (M^++H): 431.1719, found: 431.1720.

Diethyl 1,1'-(5,5'-dibromo-[1,1'-biphenyl]-2,2'-diyl)bis(1H-pyrazole-5-carboxylate) (13b). Yield: 70 % (0.35 g from 0.50 g); a brown oil; R_f = 0.16 (hexanes: EtOAc, 80:20, v/v). IR (Neat) ν_{max} 1724 (CO_2Et) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.1 Hz, 6H), 4.08 (q, J = 7.1 Hz, 4H), 6.70 (d, J = 1.9 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 1.8 Hz, 2H), 7.40-7.42 (m, 1H), 7.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 61.4, 112.1, 122.1, 129.2, 131.7, 134.3, 135.0, 135.7, 137.6, 139.8,

159.0. Mass (ESI+) *m/z* = 586.9. ESI-HRMS calcd. for $C_{24}H_{21}Br_2N_4O_4$ (M^++H): 586.9930, found: 586.9931.

Diethyl 1,1'-(biphenyl-2,2'-diyl)bis(5-methyl-1*H*-pyrazole-4-carboxylate) (16a). Yield: 78 % (0.31 g from 0.39 g); a white solid; mp 172-174 ^oC; R_f = 0.20 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1708 (CO_2Et) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 6.7 Hz, 6H), 2.38 (s, 6H), 4.27 (q, *J* = 6.7 Hz, 4H), 7.09 (brs, 2H), 7.22-7.26 (m, 2H), 7.32 (t, *J* = 7. 3 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.81 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 11.9, 14.5, 60.0, 112.4, 128.2, 128.7, 129.2, 131.4, 135.6, 136.8, 141.6, 145.2, 163.9. Mass (ESI+) *m/z* = 459.3. ESI-HRMS calcd. for $C_{26}H_{27}N_4O_4$ (M^++H): 459.2032, found: 459.2035.

Diethyl 1,1'-(5,5'-dibromobiphenyl-2,2'-diyl)bis(5-methyl-1*H*-pyrazole-4-carboxylate) (16b). Yield: 80 % (0.42 g from 0.52 g); an off white solid; mp 196-198 ^oC; R_f = 0.45 (hexanes: EtOAc, 60:40, v/v). IR (KBr) ν_{max}: 1702 (CO_2Et) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 6H), 2.22 (s, 6H), 4.21(q, *J* = 7.1 Hz, 4H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.28 (s, 2H), 7.46 (dd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 2H), 7.74 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 11.8, 14.5, 60.1, 112.9, 123.0, 129.2, 132.2, 134.6, 135.7, 136.3, 141.9, 145.0, 163.6. Mass (ESI+) *m/z* = 615.0. ESI-HRMS calcd. for $C_{26}H_{25}Br_2N_4O_4$ (M^++H): 615.0243, found: 615.0245.

2-(3-Methyl-5-phenyl-1*H*-pyrazol-1-yl)phenol (18). Yield: 7 % (0.03 g from 0.40 g); a white solid; mp 145-147 ^oC; R_f = 0.50 (hexanes: EtOAc, 80:20, v/v). IR (KBr) ν_{max} 1722 (CO_2Et), 3398 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3H), 6.23 (s, 1H), 6.49-6.53 (m, 1H), 6.56-6.58 (m, 1H), 7.04 (d, *J* = 3.6 Hz, 2H), 7.18-7.21 (m, 2H), 7.25-7.28 (m, 3H), 9.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.7, 108.3, 118.6, 119.2, 124.3, 125.6, 128.1, 128.7, 128.8, 129.0, 130.6, 144.5, 149.8, 150.7. Mass (ESI+) *m/z* = 251.2. ESI-HRMS calcd. for $C_{16}H_{15}N_2O$ (M^++H): 251.1184, found: 251.1187.

General procedure for oxidative *ortho*-hydroxylation in *N*-aryl pyrazoles 5b, 5d, 5m, 8h, 11a-c, 14a-d, 17 for the synthesis of 6b, 6d, 6m, 8h and 18 as exemplified for the synthesis of 6b.

A 50 mL sealed-tube charged with **5b** (0.112 g, 0.34 mmol), $K_2S_2O_8$ (0.184 g, 0.68 mmol), $Pd(OAc)_2$ (0.004 g, 0.017 mmol), TFA (9.0 mL) and TFAA (1.0 mL) was heated at 90 ^oC for 12 h. Following

similar experimental procedure as reported for **3a**, a crude product was obtained which was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford the pure **6b** (0.085 g, 71 %) as a brown oil and **7b** (0.003 g, 3%) as a white solid.

Ethyl 1-(2,6-dihydroxyphenyl)-1*H*-pyrazole-3-carboxylate (21). Yield: 55 % (0.047 g from 0.074 g); a brown solid; mp 127-129 ^{o}C; R_f = 0.53 (hexanes: EtOAc, 60:40, v/v). IR (KBr) ν_{max} 1728 (CO_2Et), 3413 (OH) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.30 (t, J = 7.1 Hz, 3H), 4.28 (q, J = 7.1 Hz, 2H), 6.46 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 2.3 Hz, 1H), 7.09 (t, J = 8.2 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 9.86 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 14.3, 60.1, 106.6, 108.0, 116.4, 130.1, 134.8, 143.0, 154.3, 161.9. Mass (ESI+) *m/z* = 249.1. ESI-HRMS calcd. for $C_{12}H_{13}N_2O_4$ (M^++H): 249.0875, found: 249.0876.

ACKNOWLEDGMENT. Two of the authors (HB and SB) acknowledge the financial support in the form of fellowship from CSIR, New Delhi. Authors acknowledge the SAIF division for providing the spectroscopic data and Dr. S. Kanojiya for carrying out the detailed LC-MS studies. Authors also acknowledge the anonymous reviewers for fruitful comments and suggestions for improving the manuscript.

NOTE. † Both have equally contributed to this work.

This is CDRI Communication No. 127/2015/SB.

SUPPORTING INFORMATION. X-ray crystallographic data (CIF files), ORTEP drawings for **3p**, **6l** and **7b** and copies of ^{1}H and ^{13}C-NMR spectra of all products are included. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES

1. Zablocki, J.; Palle, V.; Blackburn, B.; Elzein, E.; Nudelman, G.; Gothe, S.; Gao, Z.; Li, Z.; Meyer, S.; Belardinelli, L. *Nucleos. Nucleot. Nucl.* **2001**, *20*, 343−360. (b) Cui, J. J.; Tran-Dubé, M.; Shen, H.; Nambu, M.; Kung, P.-P.; Pairish, M.; Jia, L.; Meng, J.; Funk, L.; Botrous, I.; McTigue, M.; Grodsky,

N.; Ryan, K.; Padrique, E.; Alton, G.; Timofeevski, S.; Yamazaki, S.; Li, Q.; Zou, H.; Christensen, J.; Mroczkowski, B.; Bender, S.; Kania, R. S.; Edwards, M. P. *J. Med. Chem*. **2011**, *54*, 6342−6363. (c) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem*. **1997**, *40*, 1347−1365. (d) Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819−1824.

2. (a) Küçükgüzel, Ş .G.; Şenkardeş, S. *Eur. J. Med. Chem*. **2015**, *97*, 786–815. (b) Miller, Z.; Kim, K.-S.; Lee, D.-M.; Kasam, V.; Baek, S. E.; Lee, K. H.; Zhang, Y.-Y.; Ao, L.; Carmony, K.; Lee, N.-R.; Zhou, S.; Zhao, Q.; Jang, Y.; Jeong, H.-Y.; Zhan, C.-G.; Lee, W.; Kim, D.-E.; Kim, K. B. *J. Med. Chem.* **2015**, *58*, 2036-2041. (c) Munier-Lehmann, H.; Lucas-Hourani, M.; Guillou, S.; Helynck, O.; Zanghi, G.; Noel, A.; Tangy, F.; Vidalain, P.-O.; Janin, Y. L. *J. Med. Chem.* **2015**, *58*, 860-877. (d) Khloya, P.; Kumar, S.; Kaushik, P.; Surain, P.; Kaushik, D.; Sharma, P. K. *Bioorg. Med. Chem. Lett.* **2015**, *25,* 1177-1181. (e) Suzuki, R.; Nozawa, D.; Futamura, A.; Nishikawa-Shimono, R.; Abe, M.; Hattori, N.; Ohta, H.; Araki, Y.; Kambe, D.; Ohmichi, M.; Tokura, S.; Aoki, T.; Ohtake, N.; Kawamoto, H. *Bioorg. Med. Chem.* **2015**, *23,* 1260-1275

3. Reviews on pyrazole synthesis: (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev*. **2011**, *111*, 6984−7034. (b) Li, M.; Zhao, B.-X. *Eur. J. Med. Chem*. **2014**, *85,* 311−340. (c) Chakroborty, S.; Bhanja, C.; Jena, S. *Heterocycl. Commun*. **2013,** *19*, 79−87. (d) Yet, L. Chapter 5.4-Five-Membered Ring Systems: With More than One N Atom. In *Progress in Heterocyclic Chemistry*; Gordon, W. G., John, A. J., Eds.; Elsevier: 2012; Vol. *24*, pp 243−279. Some recent papers on pyrazole synthesis (e) Bharathiraja, G.; Sengoden, M. Kannan, M.; Punniyamurthy, T. *Org. Biomol. Chem.* **2015**, *13*, 2786-2792. (f) Zhang, Q.; Meng, L.-G.; Wang, K.; Wang, L. *Org. Lett.* **2015**, *17*, 872-875. (g) Schmitt, D. C.; Taylor, A. P.; Flick, A. C.; Kyne, Jr. R. E. *Org. Lett.* **2015**, *17*, 1405-1408 . (h) Mykhailiuk, P. K. *Angew. Chem. Int. Ed*. **2015**, *54*, 6558–6561. (i) Zhang, Y.; Wu, S.; Wang, S.; Fang,

K.; Dong, G.; Liu, N.; Miao, Z.; Yao, J.; Li, J.; Zhang, W.; Sheng, C.; Wang, W. *Eur. J. Org. Chem*. **2015**, 2030–2037. (j) Marković, V.; Joksović, M. D. *Green Chem*. **2015**, *17*, 842-847. (k) Vanjari, R.; Guntreddi, T.; Kumar S.; Singh, K. N. *Chem. Commun*. **2015**, *51*, 366-369. (l) Guo, C.; Sahoo, B.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17402-17405. (m) Iaroshenko, V. O.; Gevorgyan, A.; Davydova, O.; Villinger, A.; Langer, P. *J. Org. Chem.* **2014**, *79*, 2906-2915. (n) Chen, Y.-C.; Zhu, M.-K.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 2712–2715.

4. (a) Nag, S.; Nayak, M.; Batra, S. *Adv. Synth. Catal*. **2009**, *351*, 2715–2723. (b) Nayak, M.; Batra, S. *Adv. Synth. Catal*. **2010**, *352*, 3431–3437. (c) Nayak, M.; Rastogi, N.; Batra, S. *Eur. J. Org. Chem*. **2012**, 1360–1366. (d) Nayak, M.; Batra, S. *RSC Adv*. **2012**, *2*, 3367–3373. (e) Nayak, M.; Batra, S. *Eur. J. Org. Chem*. **2012**, 3677–3683. (f) Nayak, M.; Batchu, H.; Batra, S. *Tetrahedron Lett*. **2012**, *53*, 4206–4208. (g) Nayak, M.; Rastogi, N.; Batra, S. *Tetrahedron* **2013**, *69*, 5029–5043. (h) Batchu, H.; Bhattacharyya, S.; Batra, S. *Org. Lett*. **2012**, *14*, 6330-6333. (i) Bhowmik, S.; Pandey, G.; Batra, S. *Chem. Eur. J*. **2013**, 19, 10487–10491. (j) Pandey, G.; Bhowmik, S.; Batra, S. *Org. Lett*. **2013**, *15*, 5044–5047. (k) Batchu, H.; Batra, S. *Tetrahedron Lett.* **2014**, *55*, 6236-6239.

5. Ohyama, M.; Tabata, Y.; Iida, M.; Kaneda, K.; Takahata, S., WO 2012102404, **2012**; *Chem. Abstr*. 157:295142.

6. Kawahara, K.; Kan, N.; Nozawa, S.; Matsuo, K. World Patent **2014**, WO 2014021284; *Chem. Abstr.*160:269304.

7. Furuta, Y.; Komatsu, K.; Kaya, A.; Takahata, S.; Tabata, Y. US Patent **2014**, US 20140030209; *Chem. Abstr.* **2014**, *160*, 248882.

8. Brodney, M. A. World Patent **2012**, WO 2012172449, *Chem. Abstr.* **2012**, *158*, 77258.

9. Su, M.; Tomás-Gamasa, M.; Serdjukow, S.; Mayer, P.; Carell, T. *Chem. Commun.* **2014**, *50*, 409-411.

10. For reviews on C−H activation see: (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514. (b) Bergman, R. G. *Nature* **2007**, *446*, 391–393. (c) Yu, J.-Q., Shi, Z.-J., Eds.; *Topics in Current Chemistry*, Vol. 292; Springer: Berlin, **2010**. (d) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (e) Willis, M. C. *Chem. Rev*. **2010**, *110*, 725–748. (f) Colby, D. A. Bergman, R. G. Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624–655. (g) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214. (h) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (i) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev*. **2011**, *111*, 1780–1824. (j) Sun, C.-L.; Li, B.-J.; Shi. Z.-J. *Chem. Rev*. **2011**, *111*, 1293–1314. (k) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 8960–9009. (l) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res*. **2012**, *45*, 788–802. (m) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588–5598. (n) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814–825. (o) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev*. **2012**, *41*, 3464–3484. (p) Wang, C. *Synlett* **2013**, *24*, 1606–1613. (p) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed*. **2014**, *53*, 74–100. (q) Rao, Y.; Shan, G.; Yang, X. L. *Sci. China. Chem*. **2014**, *57*, 930–944. (r) Zheng, Q.-Z.; Jiao, N. *Tetrahedron Lett*. **2014**, *55*, 1121–1126. (s) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461–1479.

11. (a) Lyon, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110,* 1147–1169. (b) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936-946.

12. For ortho C-H functionalization in 1-phenylpyrazole see (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (b) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619–2622. (c) Kalberer, E. W.; Whitfield, S. R.; Sanford, M. S. *J. Mol. Catal. A: Chem.* **2006**, *251*, 108–113. (d) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634-12635. (e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905. (f) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org Lett.* **2009**, *11*, 4716–4719. (g) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem. Int. Ed*. **2010**, *49*, 6629–6632. (h) Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251–1253. (i) Hashimoto, Y.; Hirano, K.; Satoh, T.;

Kakiuchi, F.; Miura, M. *J. Org. Chem.* **2013**, *78*, 638–646. (j) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org Lett.* **2012**, *14*, 2146–2149. (k) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110–9113. (l) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Org Lett.* **2012**, *14*, 4262–4265. (m) Tang, C.; Yuan, Y.; Cui, Y.; Jiao, N. *Eur. J. Org. Chem.* **2013**, 7480–7483. (n) Zhou, B.; Du, J.; Yang, Y.; Feng, H.; Li, Y. *Org Lett.* **2014**, *16*, 592–595. (o) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L. *Org Lett.* **2013**, *15*, 3286–3289. (p) Tang, R.-J.; Luo, C.-P.; Yang, L.; Li, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 869–873. (q) Lou, S.-J.; Xu, D.-Q.; Xia, A.-B.; Wang, Y.-F.; Liu, Y.-K.; Du, X.-H.; Xu, Z.-Y. *Chem. Commun.* **2013**, *49*, 6218–6220. (r) Xie, F.; Qi, Z.; Li, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 11862–11866. (s) Han, S.; Sharma, S.; Park, J.; Kim, M.; Shin, Y.; Mishra, N. K.; Bae, J. J.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2013**, *79*, 275–284. (t) Kim, S. H.; Lee, S.; Yu, J.; Kim, J. N. *Tetrahedron Lett.* **2014**, *55*, 4790-4794. (u) Lu, M.-Z.; Lu, P.; Xu, Y.-H.; Loh, T.-P. *Org Lett.* **2014**, *16*, 2614–2617. (v) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780–4787. (w) Du, J.; Yang, Y.; Feng, H.; Li, Y.; Zhou, B. *Chem. Eur. J.* **2014**, *20*, 5727–5731. (x) Yu, S.; Li, X. *Org Lett.* **2014**, *16*, 1220–1223.

13. Shi, S.; Kuang, C. *J. Org. Chem.* **2014**, *79*, 6105–6112.

14. (a) Kamal, A.; Srinivasulu, V.; Sathish, M.; Tangella, Y.; Nayak, V. L.; Rao, M. P. N.; Shankaraiah, N.; Nagesh, N. *Asian J. Org. Chem.* **2014**, *3*, 68–76. (b) Rastogi, S. K.; Medellin, D. C.; Kornienko, A. *Org. Biomol. Chem*. **2014**, *12*, 410–413 (the reaction condition for *ortho*-hydroxylation reported in this paper was reported by Rao et al. earlier ref. 15).

15. Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem. Int. Ed*. **2012**, *51*, 13070–13074.

16. (a) Oi, S.; Sato, H.; Sugawara, S.; Inoue, Y. *Org Lett.* **2008**, *10*, 1823–1826. (b) Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; H. K. Potukuchi, *Synthesis* **2010**, 2245–2253. (c) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 3075–3078.

17. Dong, J.; Liu, P.; Sun, P. *J. Org. Chem.* **2015**, *80*, 2925–2929.

18. Vera-DiVaio, M. A.; Freitas, A. C.; Castro, H. C.; de Albuquerque, S.; Cabral, L. M.; Rodrigues, C. R.; Albuquerque, M. G.; Martins, R. C.; Henriques, M. G.; Dias, L. R. *Bioorg. Med. Chem.* **2009**, *17*, 295–302.

19. Correa, A.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2673–2676.

20. Murugesan, D.; Mital, A.; Kaiser, M.; Shackleford, D. M.; Morizzi, J.; Katneni, K.; Campbell, M.; Hudson, A.; Charman, S. A.; Yeates, C. *J. Med. Chem.* **2013**, *56*, 2975–2990.

21. Albright, Jay D.; Delos, Santos Efren G.; Du, Xuemei, US 000671903, **2003**; *Chem. Abstr*. **2003**, *133*, 17487.

22. Elguero, J.; Estopa, C.; Ilavsky, D. *J. Chem. Res. (S)*. **1981**, *12*, 364–365.

23. Teo, Y.-C.; Yong, F.-F.; Poh, C.-Y.; Yan, Y.-K.; Chua, G.-L. *Chem. Commun.* **2009**, 6258–6260.

24. Yang, Q.; Wang, Y.; Yang, L.; Zhang, M. *Tetrahedron* **2013**, *69*, 6230–6233.

25. Anderson, P. L.; Paolella, N. A, US 03 04, 59474, **2003**; *Chem. Abstr*. **2003**, *98*, 53887.

26. Barbero, N.; Martin, R. *Org Lett.* **2012**, *14*, 796–799.

27. Liu, P. M.; Frost, C. G. *Org. Lett.* **2013**, *15*, 5862–5865

28. Reddy, M. M.; Kumar, M. A.; Swamy, P.; Naresh, M.; Srujana, K.; Satyanarayana, L.; Venugopal, A.; Narender, N. *Green Chem.* **2013**, *15*, 3474–3483.

29. Schmidt, A.; Habeck, T.; Kindermann, M. K.; Nieger, M. *J. Org. Chem.* **2003**, *68*, 5977–5982.

30. Alvarado, M.; Goya, P.; Macías-González, M.; Pavón, F. J.; Serrano, A.; Jagerovic, N.; Elguero, J.; Gutiérrez-Rodríguez, A.; García-Granda, S.; Suardíaz, M. *Bioorg. Med. Chem.* **2008**, *16*, 10098–10105.

31. Murray, W. V.; Wachter, M. P. *J. Heterocyclic Chem*. **1989**, *26*, 1389–1392.

32. Pandey, G.; Bhowmik, S.; Batra, S. *Org Lett.* **2013**, *15*, 5044–5047.

33. Schohe-Loop, R.; Welker, R.; Paessens, A.; Bauser, M.; Stoll, Friedrike.; D, Frank.; Henninger, Kerstin.; Paulsen, Daniela.; Lang, Dieter, WO 09 11, 5252, **2009**; *Chem. Abstr*. **2009**, *151*, 381345.

34. Sun, A.; Ye, J-H.; Yu, H.; Zhang, W.; Wang, X. *Tetrahedron Lett.* **2014**, *55*, 889–892.

35. Pommery, N.; Taverne, T.; Telliez, A.; Goossens, L.; Charlier, C.; Pommery, J.; Goossens, J.-F.; Houssin, R.; Durant, F.; Hénichart, J.-P. *J. Med. Chem.* **2004**, *47*, 6195–6206.

36. Schmidt, A.; Münster, N.; Dreger, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2790–2793.

37. McInnes, C.; Liu, S, US 13 02, 89240, **2013**; *Chem. Abstr*. **2013**, *159*, 710353.

38. Hays, D. S.; Kshirsagar, T. A, WO 07 07, 9086, **2007**; *Chem. Abstr*. **2007**, *147*, 166321.

39. Choi, G. I.; Nam, G. S.; Hwang, H. S.; Lim, H. W.; Seo, S. H.; Shin, H. S.; Kim, Dong J.; Han, H. G.; Cho, Y. S.; Bae, A. N.; Shin, G. J.; Kang, S. B.; Shin, D. Y.; Chu, H. A.; Noh, E. J, KR 09 04, 4924, **2009**; *Chem. Abstr*. **2009**, *150*, 563864.

40. Oosumi, Kazuya; Yamamoto, Masashi; Aoki, Takumi; Udagawa, Shuji; Hayashi, Kenichi, WO 14 95, 1055, **2014**; *Chem. Abstr*. **2014**, *160*, 530506.

41. Hanzlowsky, A.; Jelencic, B.; Recnik, S.; Svete, J.; Golobic, A.; Stanovnik, B. *J. Heterocyclic Chem*. **2003**, *40*, 487–498.

42. Buckman, B. O.; Nicholas, J. B.; Emayan, K.; Seiwert, S. D, WO 13 0225733, **2013**; *Chem. Abstr*. **2013**, *158*, 359755.

43. Menozzi, G.; Mosti, L.; Schenone, P. *J. Heterocyclic Chem*. **1987**, *24*, 1669–1675.

44. Li, X.; He, L.; Chen, H.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3636–3646.

45. Kumar, V.; Chang, C.-K.; Tan, K.-P.; Jung, Y.-S.; Chen, S.-H.; Cheng, Y.-S. E.; Liang, P.-H. *Org Lett.* **2014**, *16*, 5060–5063.