JOC The Journal of Organic Chemistry

Article

Chemo-, Regio- and Stereoselective N-alkenylation of Pyrazoles/ Benzpyrazoles using Activated and Unactivated Alkynes

Vineeta Garg, Pradeep Kumar, and Akhilesh K. Verma

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01746 • Publication Date (Web): 01 Sep 2017

Just Accepted

ACS Publications

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

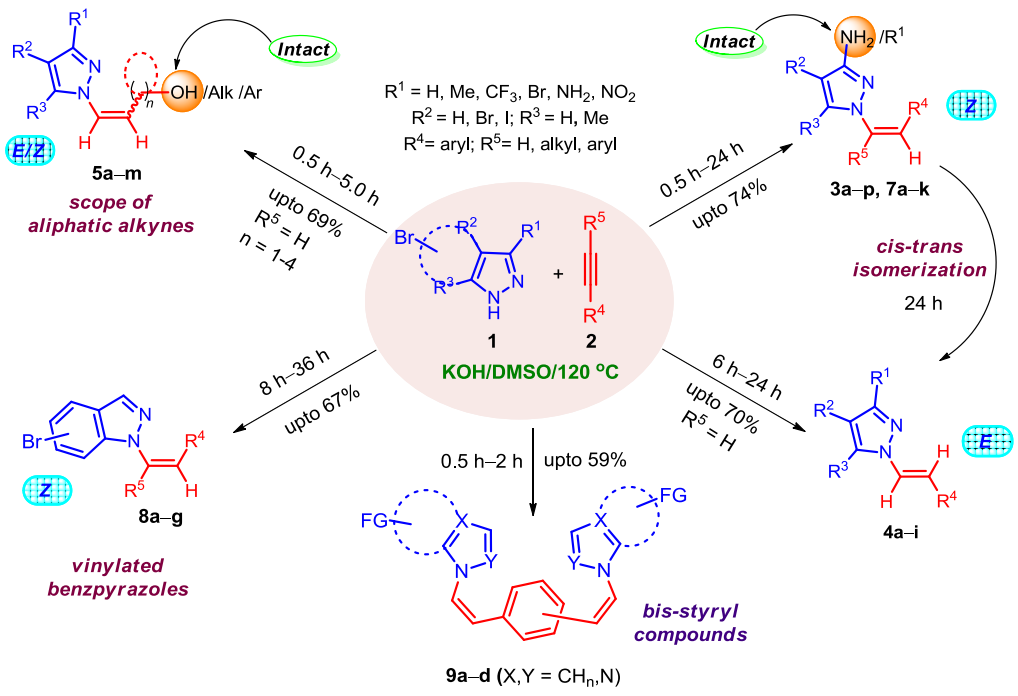
Chemo–, Regio– and Stereoselective *N*–alkenylation of Pyrazoles/Benzpyrazoles using Activated and Unactivated Alkynes

*Vineeta Garg, Pradeep Kumar and Akhilesh K. Verma**

Synthetic Organic Chemistry Research Laboratory, Department of Chemistry,

University of Delhi, Delhi–110007, India

Email: averma@acbr.du.ac.in



ABSTRACT: Transition–metal–free chemo–, regio– and stereoselective synthesis of (*Z*) and (*E*) styryl pyrazoles and benzpyrazoles by the addition of *N*–heterocycles onto functionalized terminal and internal alkynes using a super basic solution of KOH/DMSO has been described.

The stereochemical outcome of the reaction was governed by time and quantity of the base. The reaction of pyrazoles and benzpyrazoles onto alkynes takes place chemoselectively without affecting the free $–NH_2$ group of pyrazoles and –OH group of alkynes. The designed protocol was well implemented on alkynes bearing long alkyl chain, an alicyclic ring, hydroxy, ether, and ester functionality; offer the *N*–alkenylated products in good yields. This developed methodology also provides easy access for the synthesis of bis–vinylated heterocycles. The presence of free $–NH_2$, –OH, −COOR and halo group in styryl pyrazoles, could be further utilized for synthetic elaboration, which is advantageous for biological evaluation. For the first time, we have disclosed the base-mediated conversion of (*Z*)-styryl pyrazoles to (*E*) styryl pyrazoles in KOH/DMSO system. The cis–trans isomerization was supported by the control experiments and deuterium labeling studies.

INTRODUCTION

Heterocycles containing potential C–N bonds have an enormous impact on organic and medicinal chemistry.[1] In particular; alkylated pyrazoles have gained widespread interest of the researchers over the past decade due to their vast biological significance like SR144528 **(I)** is a potent and highly selective CB_2 receptor inverse agonist, MK−0893 **(II)** as a potent glucagon receptor inhibitor, ruxolitinib **(III)** as a JAK 1/2 kinase inhibitor and 3−flourophenyl urea derivative of pyrazole **(IV)** showed a good inhibition of neutrophils chemotaxis (Figure 1).[2] A broad range of pharmaceutically active ingredients like celecoxib, deracoxib, phenylbutazone, oxyphenbutazone, feprazone, and kebuzone, possess pyrazole as a core nucleus with reduced ulcer genic side effects.[3] Pyrazoles motif act as an effective analgesic,[4] antitubercular,[5] anticancer,[6] antibacterial,[7] sodium channel blocker,[8] anti–influenza,[9] antioxidant and

antimicrobial[10] agent. Significantly, pyrazole analogs are well exploited for biological systems due to their excellent stability and therefore used as a urease inhibitors,[11] monoamine oxidase,[12] and cannabinoid receptor antagonists.[13] In 2009, Vukicevic and co−workers reported the antimicrobial properties of ferrocene unit containing pyrazoles.[14] Further, the pyrazole–thiadiazole hybrids are known for selective cyclooxygenase–2 (COX–2) inhibitors due to their ability to form hydrogen bonds and a π–cation interaction with cyclooxygenase–2 (COX–2) enzyme effectively.[15]

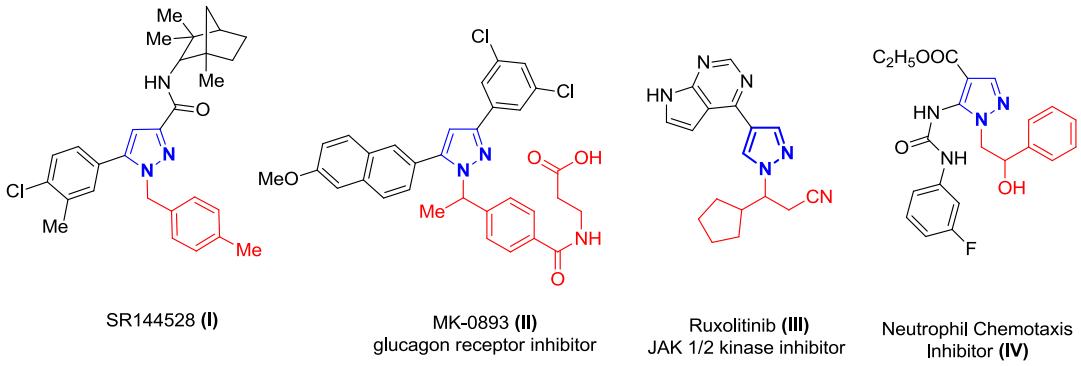
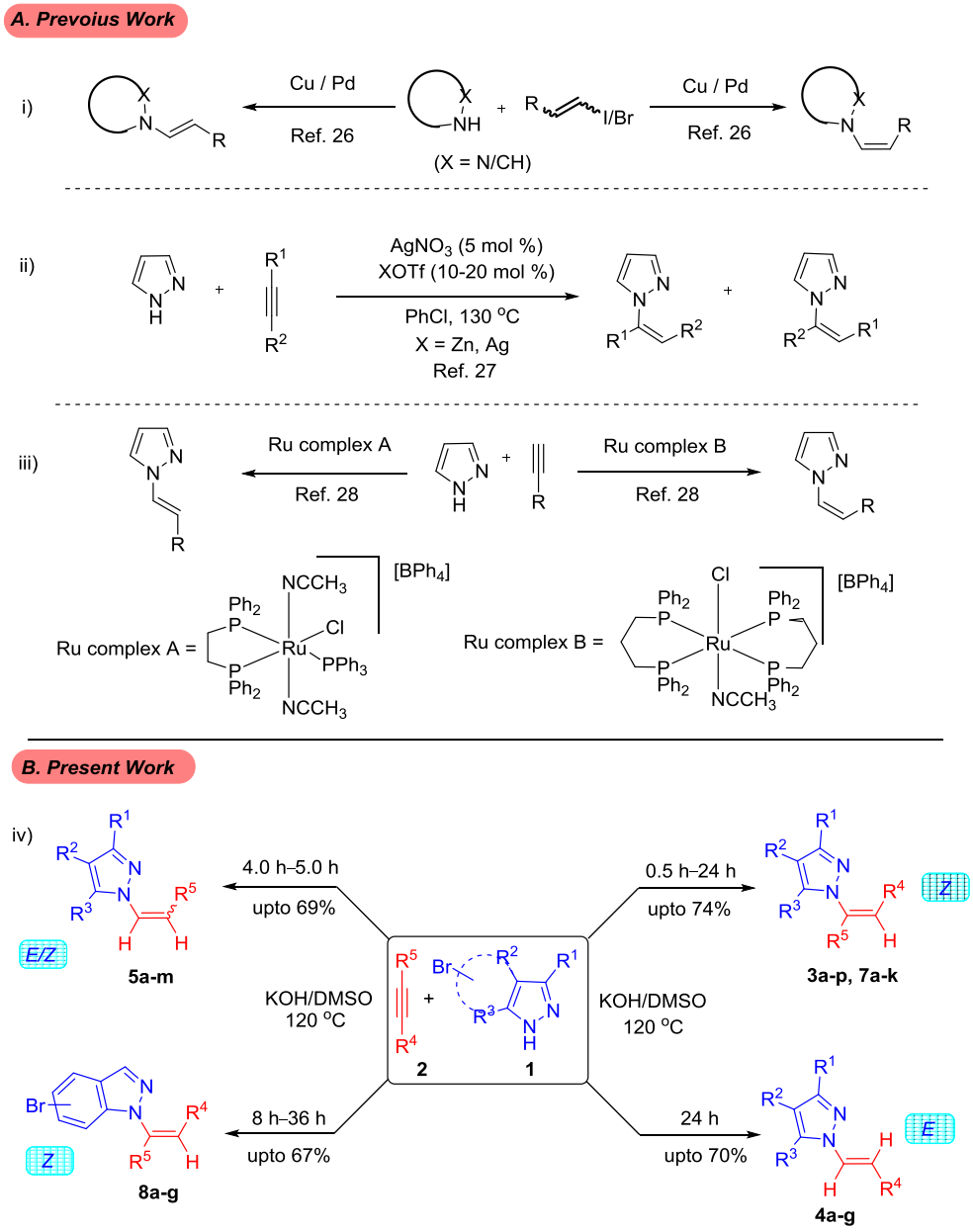


Figure 1. Biologically active compounds possessing *N*−substituted pyrazole.

Owing to the biological importance of pyrazoles analogs,[15] their synthesis has been extensively studied by various scientists.[16] However; metal−free approach for the synthesis of vinylated pyrazole under mild reaction condition remains elusive. A literature survey revealed that vinyl group is widely used for the preparation of polymeric dyes, catalysis and act as synthetic intermediates in various organic reactions.[17] The transition–metal–catalyzed inter or intramolecular hydroamination on alkynes, has been explored by Knochel,[18] Bergmann,[19] Doye,[20] Beller,[21] Yamamoto,[22] Kondo,[23] Ackermann[24] and other[25] for the synthesis of *N*–heterocycles. However, the metal–catalyzed coupling reactions of vinyl halides and vinyl boronic acids with azoles provide alternative methods for the synthesis of vinylated *N*–heterocycles (Scheme 1, i).[26]

Scheme 1. Synthesis of *N*-Styryl Pyrazoles/Azoles



In 2008, Tsuchimoto and co–workers reported the silver and zinc−catalyzed addition of N–H of pyrazoles onto alkynes using high catalyst loading (Scheme 1, ii).[27] Recently, Bhattacharjee[28] and fellow workers use ruthenium complexes $[Ru(dppe)(PPh_3)(CH_3CN)_2Cl][BPh_4]$ and $[Ru(dppp)_2(PPh_3)(CH_3CN)Cl][BPh_4]$ for the generation of *E* and *Z* isomer respectively (Scheme 1, iii). Metal–free hydroamination has been explored by Trofimov,[29] and our group[30] using super

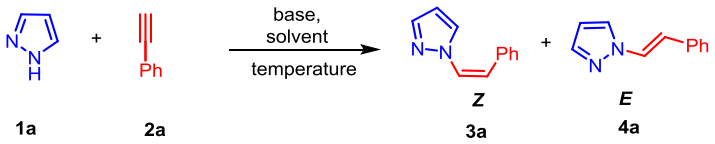
basic system (KOH/DMSO). However, the synthesis of *N*–alkenylated pyrazoles in regio–, chemo– and stereo–selective fashion with aliphatic as well as aromatic alkynes under metal–free condition is challenging.

Inspired by our previous reports on hydroamination,[30] herein, we have described a facile and versatile protocol for the construction of functionalized (*E*) and (*Z*) vinylated pyrazoles and benzpyrazoles with activated and unactivated alkynes in KOH/DMSO system (Scheme 1, iv).

RESULTS AND DISCUSSION

To identify the optimal reaction conditions, we initiated the reaction of pyrazole (**1a**) with phenyl acetylene (**2a**) using our reported conditions[30d] that is 0.2 equiv of KOH in DMSO at 120 °C for 30 min, afforded the (*Z*)−1-styryl-1*H*-pyrazole (**3a**) in 58% yield (Table 1, entry 1). Increasing the amount of base from 0.2 to 0.5 equiv, provided the (*Z*)−styryl product **3a** in 74% yield (entry 2), however; further increasing the amount of base, decreases the yield of (*Z*)−styryl product (entry 3). Thus, 0.5 equiv of the base in 30 min was found to be efficient for obtaining (*Z*)−styryl product. When the reaction was allowed to stir for 24 h using 0.5 equiv of a base mixture of stereoisomers (*Z*:*E*::70:30) was obtained in 70% yield (entry 4). Increase in the amount of base from 0.5 equiv to 1.0 equiv led to the formation of *E* isomer in the ratio (*Z*:*E*::40:60) (entry 5). Further, to obtain the *E*–selective product we increase the amount of base from 1.0 to 1.5 and then to 2.0 equiv, interestingly we obtained (*E*)−styryl product **4a** (*Z*:*E*::0:100) exclusively in 68% yield (entries 6 and 7). The lower yield was obtained with other bases such as NaOH, $CsOH.H_2O$, KO^{t}Bu, and K_3PO_4 in DMSO (entries 8–11). An organic base such as Et_3N was found to be ineffective for the reaction (entry 12). The above results confirmed that the reaction time, as well as the amount of base, was important to control the stereoselectivity of the reaction.

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a 4a

entry	alkyne	base (equiv)	solvent	time (h)/T °C	yield (%), **3a/4a** (*Z*:*E*)[b]
1[30d]	**2a**	KOH (0.2)	DMSO	0.5 / 120	58 (100:00)
2[c]	**2a**	**KOH (0.5)**	**DMSO**	**0.5 / 120**	**74 (100:00)**
3	**2a**	KOH (1.0)	DMSO	0.5 / 120	72 (100:00)
4	**2a**	KOH (0.5)	DMSO	24 / 120	70 (70:30)
5	**2a**	KOH (1.0)	DMSO	24 / 120	68 (40:60)
6	**2a**	KOH (1.5)	DMSO	24 / 120	68 (10:90)
7[c]	**2a**	**KOH (2.0)**	**DMSO**	**24 / 120**	**68 (00:100)**
8	**2a**	NaOH (0.5)	DMSO	0.5 / 120	69 (100:00)
9	**2a**	$CsOH.H_2O$ (0.5)	DMSO	0.5 / 120	62 (100:00)
10	**2a**	KO^tBu (0.5)	DMSO	0.5 / 120	60 (100:00)
11	**2a**	K_3PO_4(0.5)	DMSO	0.5 / 120	68 (100:00)
12	**2a**	Et_3N (0.5)	DMSO	0.5 / 120	NR

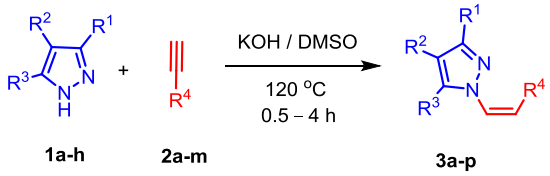
[a]Reactions were performed using pyrazole **1a** (0.5 mmol), alkyne **2a** (1.0 mmol) in 2.0 mL of solvent. [b]Sterioisomeric ratio. [c]Optimized reaction conditions for the formation of *Z*−styryl pyrazole **3a** and *E*−styryl pyrazole **4a** respectively.

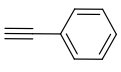
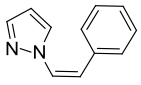
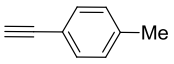
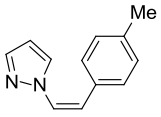
After optimizing the reaction condition, we explored the scope of substituted pyrazoles **1a-h** and alkynes **2a–m** for the synthesis of (*Z*)-styryl pyrazoles **3a–p** exclusively in good yields (Table 2, entries 1-16). The reaction of pyrazole **1a** with phenylacetylene **2a** provided the desired product **3a** in 74% yield (entry 1). When electron−releasing group containing

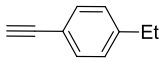
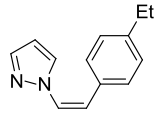
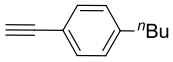
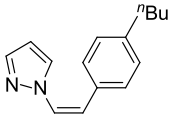
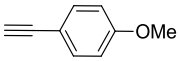
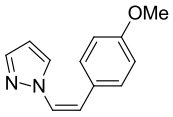
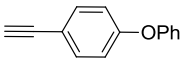
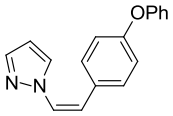
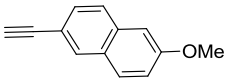
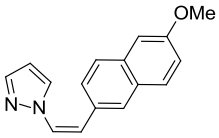
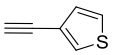
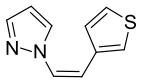
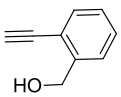
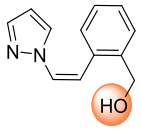
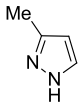
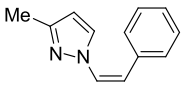
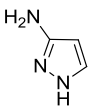
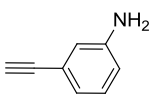
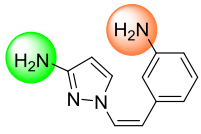
alkynes **2b–g** were used, the desired (*Z*)-styryl products **3b–g** were obtained in 67–72% yields (entries 2–7). The reaction of hetero alkyne **2h** was also successful in providing the desired product **3h** in good yield (entry 8). Interestingly, 2-ethynylphenylmethanol **2i** bearing primary alcoholic group afforded the product **3i** in 65 % yield, without affecting the free –OH group (entry 9).

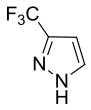
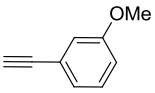
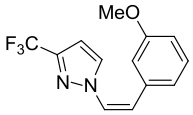
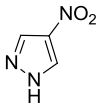
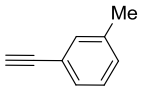
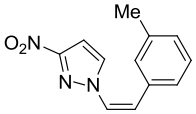
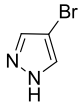
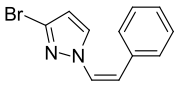
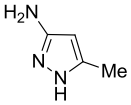
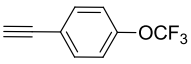
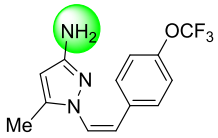
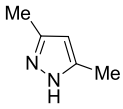
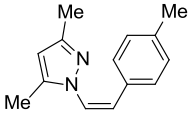
The designed methodology was well tolerated for substituted pyrazole having -CH_3 and -NH_2 functionality, and afforded the desired products **3j–k** chemoselectively in good yield without affecting free -NH_2 group (entries 10-11). Significantly, electron-withdrawing and halogen substituted pyrazoles having –CF_3, –NO_2 and –Br group afforded the hydroaminated products **3l–n** in 68-70% yields (entries 12-14). The sterically hindered pyrazoles were also reacted smoothly with substituted terminal alkynes **2m, 2b** and provided the corresponding hydroaminated products **3o** and **3p** in good yields (entries 15-16).

Table 2. Synthesis of *Z*-Styryl Pyrazoles[a]



entry	pyrazoles	alkyne 2		*(Z)* product 3		yield (%)[b]
1	 **1a**		**2a**		**3a**	74
2	**1a**		**2b**		**3b**	72

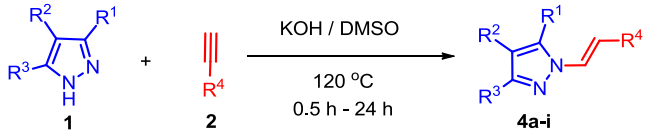
3	**1a**		**2c**		**3c**	70
4	**1a**		**2d**		**3d**	71
5	**1a**		**2e**		**3e**	68
6	**1a**		**2f**		**3f**	69
7	**1a**		**2g**		**3g**	67
8	**1a**		**2h**		**3h**	68
9	**1a**		**2i**		**3i**	65
10[c]	 **1b**		**2a**		**3j**	73
11[c]	 **1c**		**2j**		**3k**	65

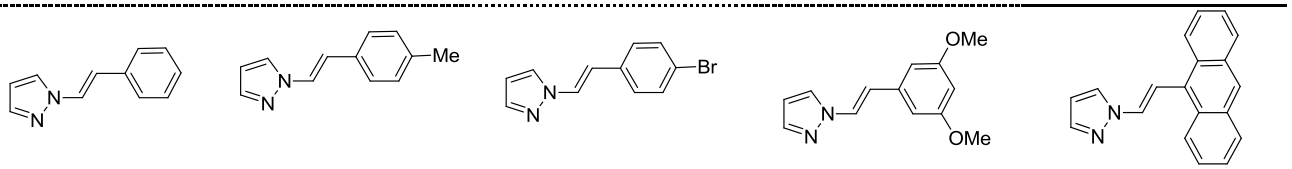
12[c]	 **1d**		**2k**		**3l**	68
13[c]	 **1e**		**2l**		**3m**	70
14[c]	 **1f**		**2a**		**3n**	68
15[c]	 **1g**		**2m**		**3o**	72
16[c]	 **1h**		**2b**		**3p**	65

[a]The reactions were performed using pyrazoles **1** (0.5 mmol), 1.0 mmol of alkynes **2**, 0.5 equiv of KOH in 2.0 mL of DMSO at 120 ^{o}C for 0.5 h. [b] Isolated yields. [c] Reaction run for 4 h.

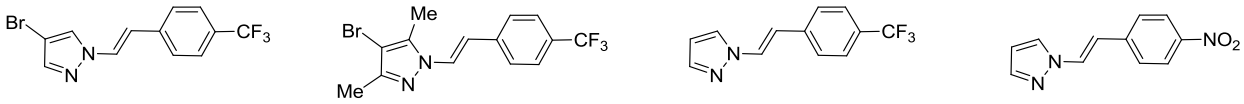
After obtaining the selective *Z*-styryl product, we extended the scope of the developed chemistry for the stereoselective synthesis of (*E*)-styryl pyrazoles **4a–g** in good yields (Scheme 2). The reaction of pyrazole **1a** with substituted alkynes **2a–b** and **2n–p** in the presence of 2.0 equiv KOH in DMSO at 120 ^{o}C for 24 h gave the *E*-styryl products **4a–e** in 65-70% yield. Electron withdrawing aryl alkynes such as 1-ethynyl-4-(trifluoromethyl)benzene **2q** and 1-ethynyl-4-nitrobenzene **2r** provided the desired *E*-styryl product **4h-i** in moderate yield with excellent selectivity.

Scheme 2. Synthesis of *E*-Styryl Pyrazoles[a]





4a, 68% **4b**, 70% **4c**, 65%[b] **4d**, 68% **4e**, 66%



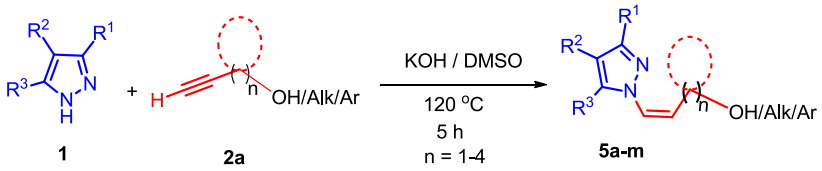
4f, 64% **4g**, 62% **4h**, 45%[c] **4i**, 50%[c]

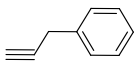
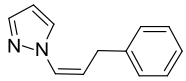
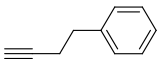
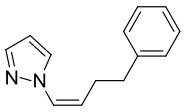
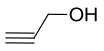
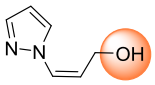
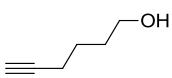
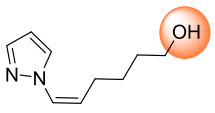
[a]The reactions were performed using pyrazoles **1** (0.5 mmol), 1 mmol of alkynes **2**, 2.0 equiv of KOH in 2.0 mL of DMSO at 120 °C for 24 h. [b]Reaction completed in 6 h.[c]Reaction run for 0.5 h with 50% recovery of starting substrate.

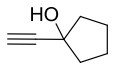
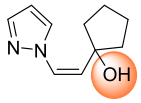
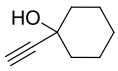
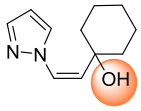
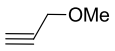
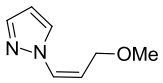
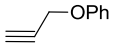
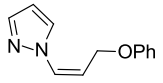
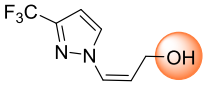
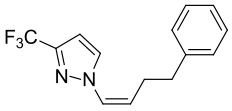
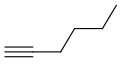
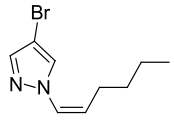
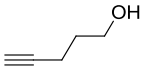
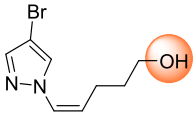
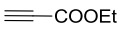
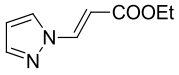
In past decades hydroamination reactions on aliphatic alkynes have been reported using expensive metal catalyst.[27-28] Therefore, we examined the developed strategy for aliphatic alkynes **2aa–ak** bearing long chain, an alicyclic ring, hydroxyl, ether, and ester group were utilized for the synthesis of *N*-alkenylated pyrazoles **5a–m** in 40-69% yields (Table 3). The reaction with aliphatic alkyne **2aa** and **2ab** provided the (*Z*)-vinylated products **5a–b** in good yields (entries 1-2). Interestingly, when a primary alcoholic group containing alkynes **2ac–ad** were employed under standard reaction conditions, the reaction gave the hydroaminated products **5c–d** in fair yields instead of hydroxylation on primary alcohol (entries 3-4). However, the reaction with 1-ethynylcyclopentanol **2ae** and 1-ethynylcyclohexanol **2af** afforded the corresponding products **5e** and **5f** in 55% and 60% yields, respectively (entries 5 and 6). Similarly, methyl and phenyl propargyl ether **2ag–ah** were also found compatible to provide the *Z*-alkenylated products **5g** and **5h** in good yields (entries 7-8). Substituted pyrazoles having

electron-withdrawing group were also successful in providing the hydroaminated products **5i–j** in 59-69% yield (entries 9-10). 4-Bromo-1*H*-pyrazole (**1f)** gave the fruitful yield of desired products **5k–l** with 1-hexyne **2ai** and 1-pentynol **2aj** (entries 12-13). Surprisingly, the reaction of ethyl propiolate **2ak** with pyrazole **1a** provided the hydroaminated product **5m** in 66% yield with absolute *E*–stereoselectivity (entry 14). The formation of *N*-alkenylated products reveals the efficacy, functional group tolerance and chemoselective behavior of designed protocol.

Table 3. Scope of Aliphatic Alkynes[a]

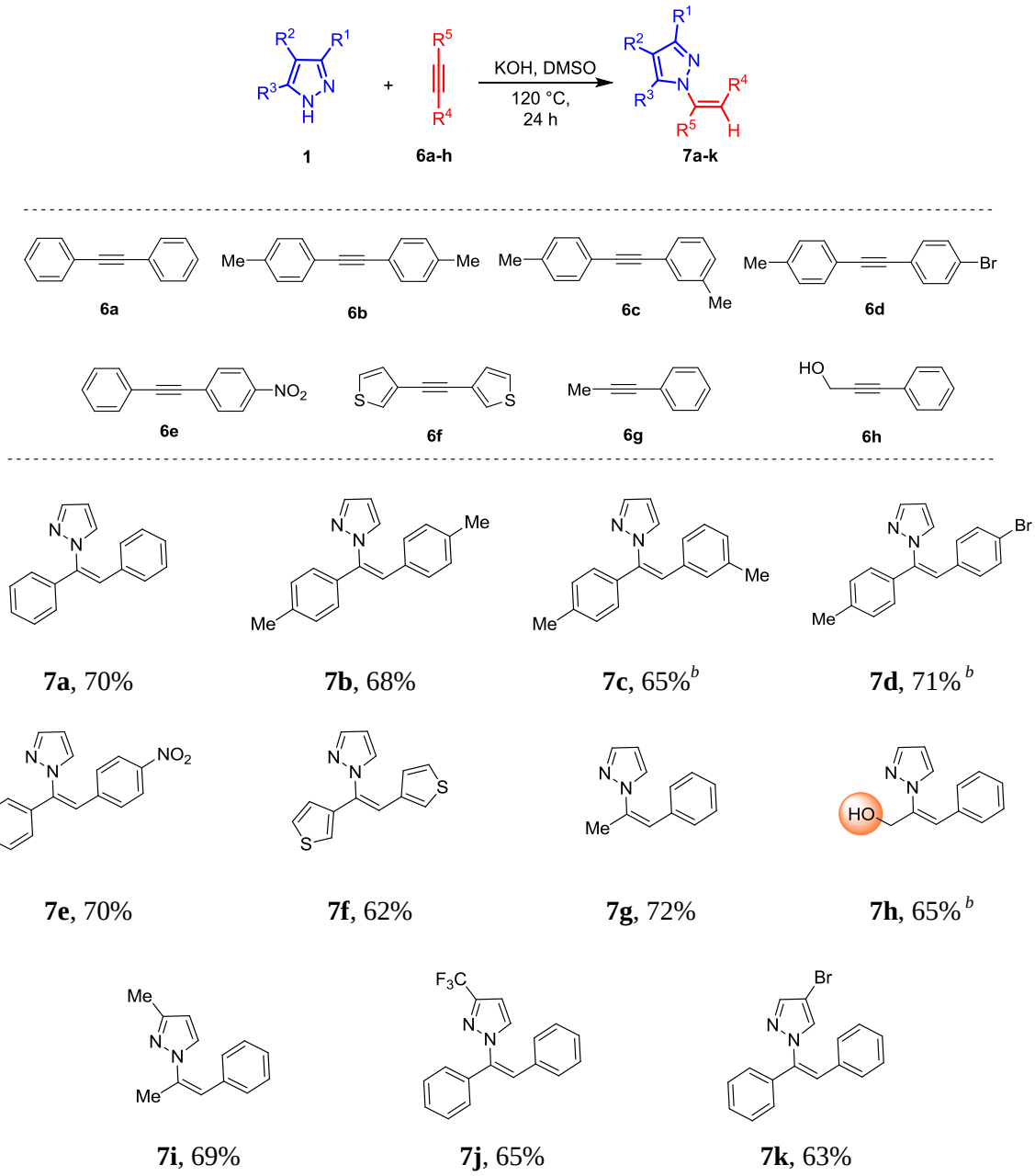


entry	pyrazoles	alkyne **2a**		product **5**		yield (%) [b]
1	**1a**		**2aa**		**5a**	62
2	**1a**		**2ab**		**5b**	60
3	**1a**		**2ac**		**5c**	68
4	**1a**		**2ad**		**5d**	58

5	**1a**		**2ae**		**5e**	55
6	**1a**		**2af**		**5f**	60
7	**1a**		**2ag**		**5g**	68
8	**1a**		**2ah**		**5h**	60
9	**1d**		**2ac**		**5i**	69
10	**1d**		**2ab**		**5j**	59
11	**1f**		**2ai**		**5k**	40
12	**1f**		**2aj**		**5l**	60
13[c]	**1a**		**2ak**		**5m**	66

[a]The reactions were performed using **1a-c** (0.5 mmol), alkyne **2** (1.0 mmol), and 1.0 equiv of KOH in 2.0 mL of DMSO at 120 [o]C for 5 h. [b] Isolated yields. [c]Reaction completed in 0.5 h.

Scheme 3. Scope of Internal Alkynes[a]



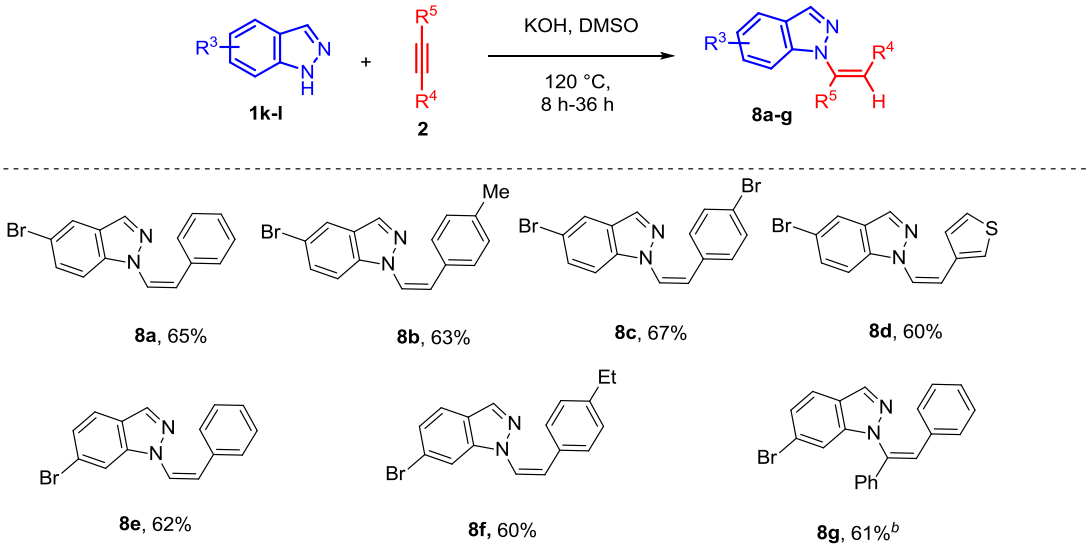
[a]The reactions were performed using pyrazoles **1** (0.5 mmol), alkynes **2** (0.5 mmol), 1.5 equiv of KOH in 2.0 mL of DMSO at 120 °C for 24 h. [b]Reaction completed in 3 h.

We next examined the scope and efficacy of the reaction by employing a wide range of substituted symmetrical and unsymmetrical internal alkynes **6a**–**h** with pyrazoles **1** to synthesize

corresponding hydroaminated product **7** in regioselective manner (Scheme 3). Nucleophilic addition of pyrazole **1a** provided the desired product **7a** with diphenylacetylene **6a** in good yields. However, 1,2-di-*p*-tolylethyne **6b** and 1-methyl-3-(*p*-tolylethynyl)benzene **6c** afforded the hydroaminated products **7b-c** in 65-68% yields. It was observed that alkyne **6d** reacted more promptly with **1a** and gave the desired product **7d** in 71% yield. Electron-withdrawing group containing alkyne **6e** yielded the addition product **7e** in 70% yield whereas electron-rich alkyne **6f** afforded the desired product **7f** in 62% yield. Aryl alkyl internal alkynes, prop-1-yn-1-ylbenzene **6g** and 3-phenylprop-2-yn-1-ol **6h,** gave the *N*-alkenylated products **7g** and **7h** in good yields. Similarly, commendable results were obtained when the reaction of 3-methyl pyrazole **1b** with alkyne **6g** was performed. The reaction of trifluoromethane substituted pyrazoles **1d** with alkyne **6a** leads to the formation of desired product **7j** in 65% yield whereas bromo substituted pyrazoles **1f** gave the product **7k** in 63% yield. The regioselectivity of the reaction was recognized by chemical shifts, coupling constants ($J_{H\text{-}H}$), and NOESY studies (see SI).

After synthesizing the library of *N*-styryl pyrazoles from differently substituted aromatic and aliphatic alkynes with pyrazoles in good yields, further efforts were carried out to explore the benzpyrazoles in the reaction. The benzpyrazoles **1k-l,** having –Br functionality reacted with terminal and internal alkynes and gave the (*Z*)-5/6-bromo-1-styryl-1*H*-indazoles **8a-g** in good yield (Scheme 4). The addition of 5-bromobenzpyrazoles **1k** on alkyne **2a** provided the product **8a** in 65% yield. However, alkyne **2b** and **2n** afforded the corresponding *Z*-addition products **8b-c** in 63-67% yield. Alkyne **2h** containing thienyl ring gave the desired product **8d** in 60% yield. Similarly, the reaction of 6 bromo-1*H*-indazoles **1l** afforded the hydroaminated products **8e** and **8f** with alkynes **2a** and **2c** in 62% and 60% yields respectively. Reactions of internal alkynes **6a** with **1k** provided the styryl products **8g** in good yield using 2.0 equiv of KOH at 120 °C for 36 h.

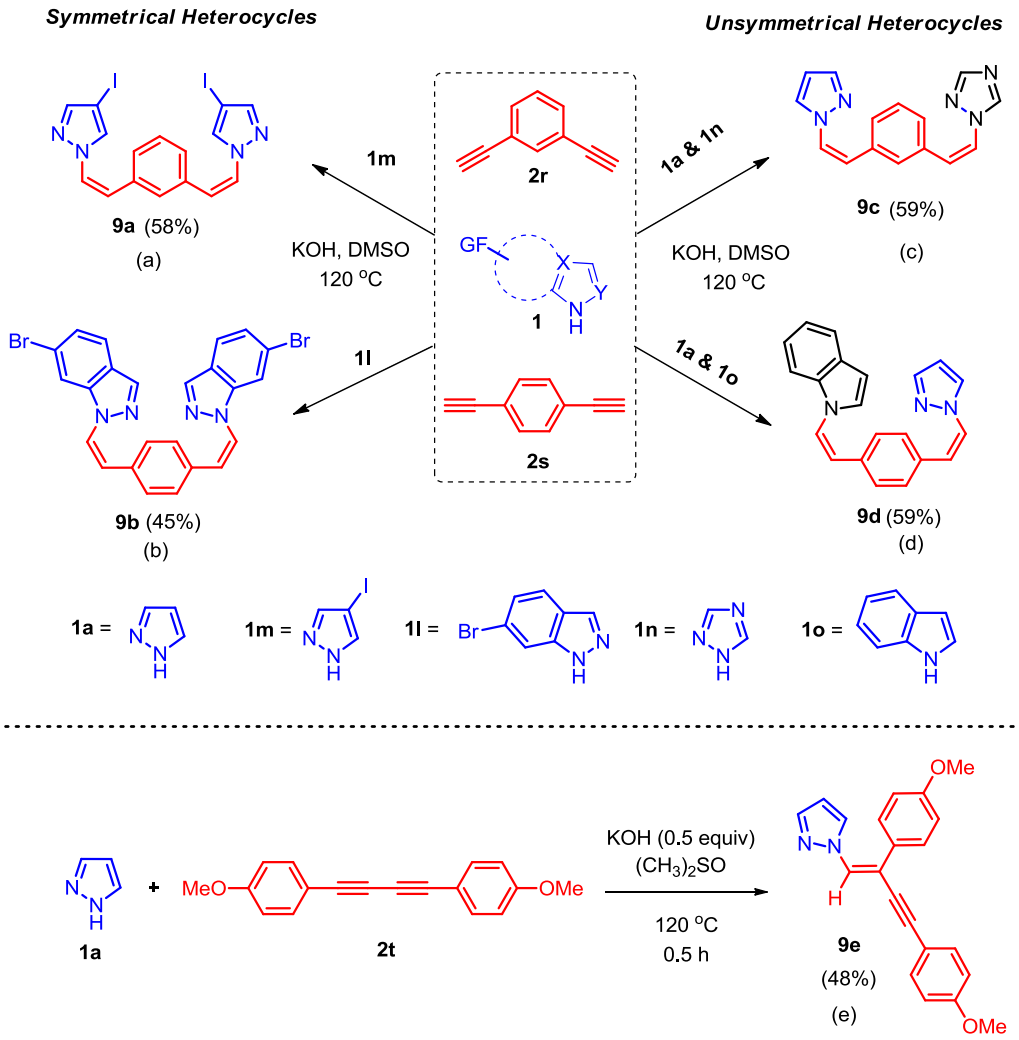
Scheme 4. Synthesis of (*Z*)-5/6-bromo-1-styryl-1*H*-indazoles[a]



[a]The reactions were performed using benzpyrazoles **1** (0.5 mmol), alkynes **2** (1.0 mmol)**,** 1 equiv of KOH in 2.0 mL of DMSO at 120 °C for 8 h. [b]benzpyrazole **1l** (0.5 mmol), alkynes **2** (0.5 mmol), 2.0 equiv of KOH for 36 h.

Encouraged by above results, we explore 1, 3 and 1, 4 diethynyl benzene **2r** and **2s** for the synthesis of bis-vinylated *N*-heterocycles compound **9a-e** (Scheme 5, a). The reaction was carried out by using 1.0 equiv of KOH at 120 °C with 4-iodo-1*H*-pyrazole **1m** for 0.5 h, provided the bis hydroaminated product **9a** in 58% yield. The reaction was also compatible with benzpyrazoles to synthesize the 1,4-bis((*Z*)-2-(6-bromo-1*H*-indazol-1-yl)vinyl)benzene **9b** in 2 h (Scheme 5, b). The reaction of triazole **1n** with alkynes **2r** along with pyrazole **1a** furnish the 1-((*Z*)-3-((*Z*)-2-(1*H*-pyrazol-1-yl)vinyl)styryl)-1*H*-1,2,4-triazole **9c** in 59% yields (Scheme 5, c). Similarly, indole **1o** and pyrazole **1a** with alkyne **2s** gave the bis-hydrominated product **9d** in good yield. Further, we elaborate the scope of reaction with 1,4-bis(4-methoxyphenyl)buta-1,3-diyne **2t** and **1a**; we obtained the hydroaminated product **9e** in 48% yield selectively (Scheme 5, e).

Scheme 5. Hydroamination on Dialkynes

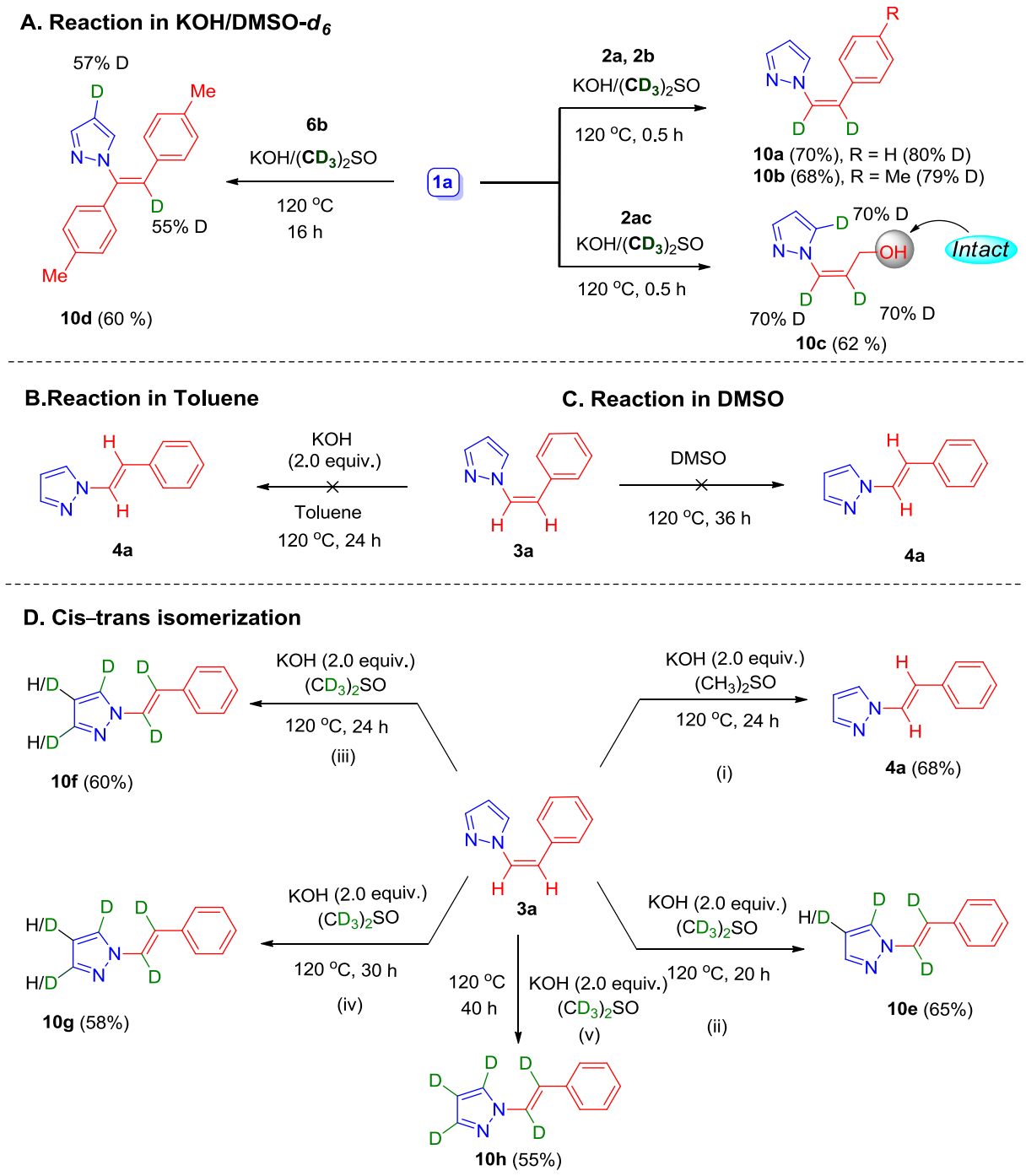


(a) The reactions were performed using pyrazole **1m** (0.5 mmol), 0.25 mmol of the alkyne **2r,** 1.0 equiv of KOH in 2.0 mL of DMSO at 120 °C for 0.5 h. (b) Benzpyrazole **1l** (0.5 mmol), 0.25 mmol of the alkyne **2s,** 1.0 equiv of KOH in 2.0 mL of DMSO at 120 °C for 2 h. (c) Pyrazole **1a** (0.5 mmol) along with triazole **1n** (0.5 mmol), 0.25 mmol of the alkyne **2r**, 1.0 equiv of KOH in 2.0 mL of DMSO at 120 °C for 2 h. (d) Pyrazole **1a** (0.5 mmol) along with indole **1o** (0.5 mmol), 0.25 mmol of the alkyne **2s**, 1.0 equiv of KOH in 2.0 mL of DMSO at 120 °C for 2 h. (e) Pyrazole **1a** (0.5 mmol), 0.25 mmol of the alkyne **2t,** 0.5 equiv of KOH in 2.0 mL of DMSO at 120 °C for 0.5 h.

Inspired by our previously reported mechanistic studies of hydrophenoxylation[31a] and hydrothiolation[31b] using KOH/DMSO system. Further, we explore the cis to trans isomerization in hydroamination. The reaction in deuterated DMSO-d_6 furnished deuterium labeled at styryl position in compounds **10a-d** indicates the source of the styryl proton was solvent (Scheme 6A). Similarly, no reaction occurs when the reaction is carried out with isolated (*Z*)-isomer **3a** using KOH/Toluene system for 36 h (Scheme 6B). These experiments confirmed that the source of styryl proton is DMSO, and experiment 6B suggested the exchange of proton was facilitating in KOH/DMSO system.

Further studies were focused on to understand the involvement of our catalyst system in cis to trans isomerization by performing the reaction in DMSO without KOH, the starting material remains unchanged (scheme 6C). This control experiment confirmed the presence of KOH/DMSO catalytic system is crucial for the reaction, probably the KOH functioning as an initiator in the scrambling of DMSO. The compound **3a** was treated with KOH/DMSO system; the *E*–product **4a** was obtained in 68% in 24 h (Scheme 6D, i). Next reaction was performed in KOH/DMSO-d_6, and the product **10e** was achieved with deuterium-labeled at styryl position (scheme 6D, ii). Further running the reaction for more time from 20 h to 24, 30 and 40 h in KOH/DMSO-d_6 provided the deuterated compounds **10f-h** in different deuterium percentage up to 100% (scheme 6C, iii-v). The Comparative ^{1}H NMR spectrum studies of cis–trans conversion in DMSO/DMSO−d_6 with various reaction intervals are shown in Figure 2.

Scheme 6. Deuterium Labeling and Control Experiments: Cis to Trans Isomerization



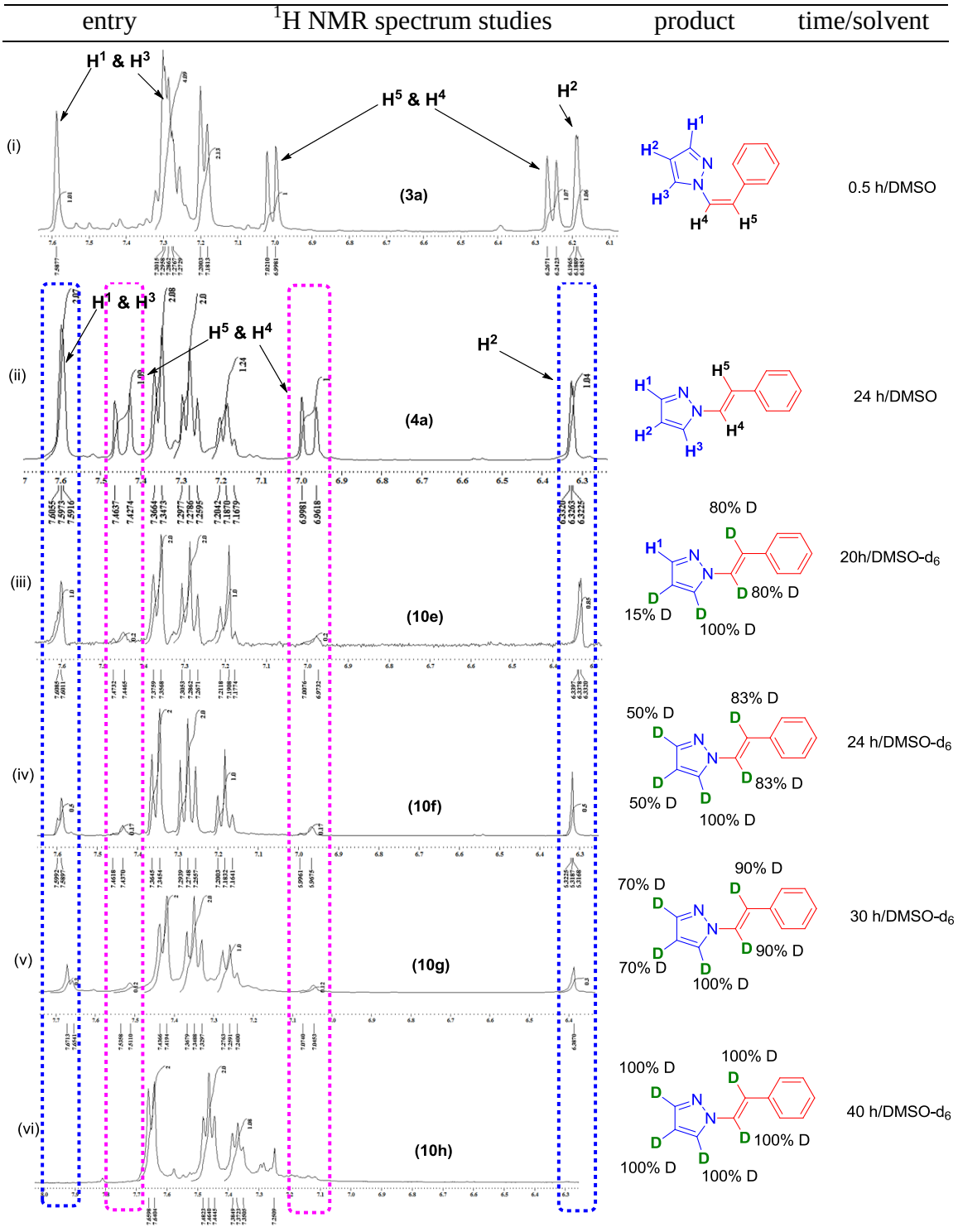
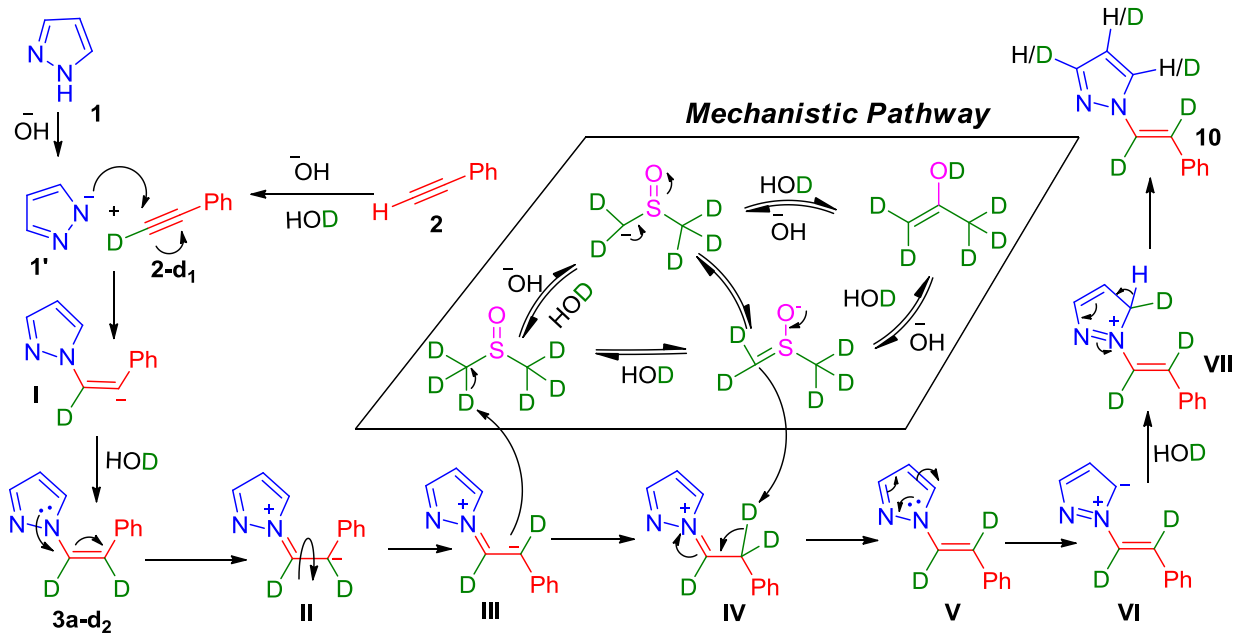


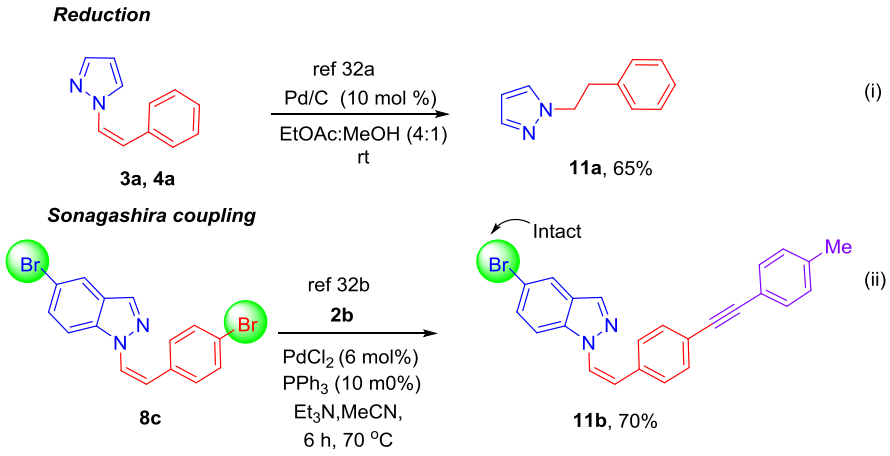
Figure 2. ^{1}H NMR Spectrum studies of cis to trans conversion and deuterium exchange in DMSO/DMSO-d_6. (i) Reaction in DMSO after 0.5 h. (ii) Reaction in DMSO after 24 h. (iii) Reaction in DMSO-d_6 after 6 h. (iv) Reaction in DMSO-d_6 after 24 h. (v) Reaction in DMSO-d_6 after 30 h. (vi) Reaction in DMSO-d_6 after 40 h.

Scheme 7. Plausible Mechanism



In the illumination of preliminary experiments, we proposed the possible mechanistic pathway for the synthesis of cis hydroaminated product **3a-d$_2$** and their conversion to trans isomer **10** via intermediate **V**. The formation of cis isomer was initiated by the attack of pyrazole anion **1'** on alkyne **2-d$_1$** to form alkenyl anion **I** (Scheme 7). Subsequently, kinetically stable *Z*-enamines **3a-d$_2$** changed into iminium ion **II** by the migration of pyrazole lone pair towards adjacent carbon. The intermediate **II** converted into intermediate **III** which after deuterium exchange generates trans isomer **V**. Further deuteration of intermediate **V** generated the compound **10** via intermediate **VI** and **VII**. The above experiments concluded that initially, the kinetic control leads to the formation of *Z* isomer but later on, the thermodynamic control converts the *Z*- to *E*-isomer.

Scheme 8. Synthetic Transformation



Having explored the variety of simple and substituted pyrazoles and benzpyrazoles with aromatic and aliphatic alkynes, further we carried out synthetic transformation of our designed *N*-vinylated pyrazoles (**3a** and **4a)** through reduction of styryl bond using 10 mol % of Pd/C in EtOAc:MeOH (4:1). Next, we diversified bromo handle compound **8c** by palladium-catalyzed Sonogashira coupling reaction (Scheme 8).

CONCLUSIONS

In summary, we have envisaged a versatile and efficient regio−, chemo− and stereoselective synthetic approach to produce a broad range of functionalized (*E*) and (*Z*) styryl pyrazole and benzpyrazole derivatives which can be used as precursors for the synthesis of biologically active molecules. We also disclosed the implementation of aliphatic alkynes in hydroamination using metal and ligand-free protocol. This method provides the simplest way for the synthesis of symmetrical and unsymmetrical bis-vinylated heterocyclic compounds. Deuterium labeling and control experiments demonstrate the role of KOH/DMSO catalytic system in the cis-trans isomerization, which was further supported by comparative ^{1}H NMR spectrum studies in DMSO/DMSO−d_6.

EXPERIMENTAL SECTION

General Information and Method. All the reactions were performed in an oven-dried Schlenk flask under an argon atmosphere. Column chromatography was performed using silica gel (mesh 100-200). TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining over I_2 chamber. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, br s = broad singlet), coupling constants in Hertz, and integration. High−resolution mass spectra were recorded with q−TOF electrospray mass spectrometer. All purchased chemicals were used as received. All melting points are uncorrected.

General procedure for the synthesis of (*Z*)−styryl pyrazoles (3a–p): In an oven dried pressure tube, to a solution of pyrazoles **1a**–**h** (0.5 mmol) in DMSO, finely crushed KOH (0.5 equiv) and alkynes **2a**–**m** (1.0 mmol) were added under inert atmosphere. The resulting reaction mixture was heated at 120 °C for 30 min. Progression of the reaction was monitored by TLC, while noticing complete consumption of alkynes, reaction was brought to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel mesh size 100–200 (hexane).

*(Z)−1−Styryl−1H−pyrazole (**3a**)*. The product was obtained as yellow oil (62.9 mg, 74% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.30–7.27 (m, 4H), 7.20–7.18 (m, 2H), 7.00 (d, *J* =

9.7 Hz, 1H), 6.25 (d, *J* = 9.7 Hz, 1H), 6.19–6.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 134.3, 129.4, 128.61, 128.56, 127.8, 126.9, 118.9, 106.6; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_{11}N_2$ 171.0922; found 171.0915.

*(Z)−1−(4−Methylstyryl)−1H−pyrazole (**3b**).* The product was obtained as a yellow semi–solid (66.2 mg, 72% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.245–7.240 (m, 1H), 7.02–6.96 (m, 4H), 6.86 (d, *J* = 9.1 Hz, 1H), 6.14–6.09 (m, 2H), 2.23 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 137.6, 131.2, 129.4, 129.1, 128.4, 126.3, 119.3, 106.4, 21.1; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{13}N_2$ 185.1079; found 185.1080.

*(Z)−1−(4−Ethylstyryl)−1H−pyrazole (**3c**).* The product was obtained as a pale yellow oil (69.3 mg, 70% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.484–7.482 (m, 1H), 7.246–7.240 (m, 1H), 7.03–6.98 (m, 4H), 6.85 (d, *J* = 9.7 Hz, 1H), 6.11 (d, *J* = 9.7 Hz, 1H), 6.08 (t, *J* = 1.8 Hz, 1H), 2.52 (q, *J* = 7.3 Hz, 2H), 1.12 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 140.0, 131.4, 129.4, 128.6, 128.0, 126.3, 119.4, 106.4, 28.5, 15.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{15}N_2$ 199.1235; found 199.1226.

*(Z)−1−(4−Butylstyryl)−1H−pyrazole (**3d**).* The product was obtained as a pale yellow oil (80.2 mg, 71% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.356–7.351 (m, 1H), 7.12–7.07 (m, 4H), 6.96 (d, *J* = 9.1 Hz, 1H), 6.25–6.20 (m, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 1.58–1.55 (m, 2H), 1.38–1.34 (m, 2H), 0.94–0.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 140.2, 131.5, 129.50, 128.62, 128.55, 126.4, 119.5, 106.5, 35.4, 33.4, 23.3, 13.9; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{19}N_2$ 227.1548; found 227.1557.

*(Z)−1−(4−Methoxystyryl)−1H−pyrazole (**3e**).* The product was obtained as a brown oil (68.0 mg, 68% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.287–7.281 (m, 1H), 7.02 (d, *J* =

8.2 Hz, 2H), 6.84 (d, *J* = 10.8 Hz, 1H), 6.74 (d, *J* = 9.6 Hz, 2H), 6.15–6.13 (m, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 140.1, 130.0, 129.5, 126.5, 125.7, 119.8, 113.9, 106.4, 55.2. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{13}N_2O$ 201.1028; found 201.1017.

*(Z)−1−(4−Phenoxystyryl)−1H−pyrazole (**3f**).* The product was obtained as colorless oil (90.3 mg, 69% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.594–7.591 (m, 1H), 7.378–7.372 (m, 1H), 7.33 (t, *J* = 8.3 Hz, 2H), 7.14–7.10 (m, 3H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 9.7 Hz, 1H), 6.91–6.89 (m, 2H), 6.22–6.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 156.4, 140.2, 130.2, 129.7, 129.4, 128.8, 126.2, 123.6, 119.2, 118.9, 118.3, 106.6; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{15}N_2O$ 263.1184; found 263.1178.

*(Z)−1−(2−(6−Methoxynaphthalen−2−yl)vinyl)−1H−pyrazole (**3g**).* The product was obtained as a pale yellow solid (83.7 mg, 67% yield), mp 91–94 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.60 (m, 1H), 7.58 (d, *J* = 4.8 Hz, 1H), 7.55 (s, 2H) 7.277–7.271 (m, 1H), 7.12–7.10 (m, 1H), 7.06 (dd, *J* = 9.1 and 2.4 Hz, 1H), 7.029–7.024 (m, 1H), 6.98 (d, *J* = 9.7 Hz, 1H), 6.32 (d, *J* = 9.7 Hz, 1H), 6.12–6.11 (m, 1H), 3.84 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 140.2, 134.0, 129.7, 129.5, 129.4, 128.8, 127.9, 127.0, 126.8, 126.6, 119.7, 119.2, 106.6, 105.7, 55.3; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{16}H_{14}N_2ONa$ 273.1004; found 273.1006.

*(Z)−1−(2−(Thiophen−3−yl)vinyl)−1H−pyrazole (**3h**).* The product was obtained as a yellow semi–solid (59.8 mg, 68% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.56 (m, 1H), 7.37–7.36 (m, 1H), 7.18–7.14 (m, 2H), 6.83 (d, *J* = 9.1 Hz, 1H), 6.73 (dd, *J* = 4.8 and 1.2 Hz, 1H), 6.22–6.21 (m, 1H), 6.19 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 134.0, 129.4, 127.8, 127.3, 126.0, 123.7, 119.1, 107.2; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_9H_8N_2SNa$ 199.0306; found 199.0306.

(Z)−(2−(2−(1H−Pyrazol−1−yl)vinyl)phenyl)methanol (***3i***). The product was obtained as yellow solid (65.0 mg, 65% yield), mp 91–94 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.49 (m, 2H), 7.34 (t, J = 6.8 Hz, 1H), 7.27–7.23 (m, 1H), 7.14–7.13 (m, 1H), 7.13–7.11 (m, 1H), 7.07 (d, J = 2.2 Hz, 1H), 6.31 (d, J = 9.9 Hz, 1H), 6.12 (t, J = 2.2 Hz, 1H), 4.61 (s, 2H), 2.52 (br s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 138.9, 133.4, 129.2, 128.8, 128.22, 128.17, 127.9, 115.1, 107.0, 63.1; HRMS (ESI^{-}TOF) *m/z*: $(M+H)^{+}$ Calcd for $C_{12}H_{13}N_2O$ 201.1028; found 201.1024.

(Z)−3−Methyl−1−styryl−1H−pyrazole (***3j***)**.** The product was obtained as a yellow semi–solid (67.1 mg, 73% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.24–7.22 (m, 3H), 6.95–6.94 (m, 2H), 6.81 (d, J = 9.1 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 6.08 (s, 1H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 134.7, 130.2, 128.9, 128.7, 128.6, 127.6, 117.4, 106.6, 13.5; HRMS (ESI^{-}TOF) *m/z*: $(M+H)^{+}$ Calcd for $C_{12}H_{13}N_2$ 185.1079; found 185.1080.

(Z)−1−(3−Aminostyryl)−1H−pyrazol−4−amine (***3k***)**.** The product was obtained as a yellow semi–solid (65.0 mg, 65% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 2.2 Hz, 1H), 7.09–7.05 (m, 1H), 6.69 (d, J = 9.9 Hz, 1H), 6.64 (d, J = 7.6 Hz, 1H), 6.56–6.54 (m, 2H), 5.93 (d, J = 9.9 Hz, 1H), 5.55 (d, J = 3.0 Hz, 1H), 3.64 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 146.5, 135.9, 131.1, 129.4, 126.4, 118.9, 115.6, 114.9, 114.2, 95.3; HRMS (ESI^{-}TOF) *m/z*: $(M+H)^{+}$ Calcd for $C_{11}H_{13}N_4$ 201.1140; found 201.1135.

(Z)−1−(3−Methoxystyryl)−3−(trifluoromethyl)−1H−pyrazole (***3l***). The product was obtained as a yellow oil (91.1 mg, 68% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.19–7.15 (m, 1H), 6.91 (d, J = 9.1 Hz, 1H), 6.78 (dd, J = 8.5 and 2.4 Hz, 1H), 6.69 (d, J = 7.9 Hz, 1H), 6.60 (s, 1H), 6.38–6.34 (m, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 134.6, 131.3,

130.0, 126.4, 122.4, 122.3, 121.0, 114.5, 113.4, 105.0, 55.1; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{12}F_3N_2O$ 269.0902; found 269.0909.

(Z)−1−(3−Methylstyryl)−4−nitro−1H−pyrazole ***(3m).*** The product was obtained as a yellow semi–solid (80.1 mg, 70% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.91 (s, 1H), 7.16 (t, J = 8.3 Hz, 1H), 7.08–7.07 (m, 1H), 6.91 (s, 1H), 6.87–6.82 (m, 2H), 6.45 (d, J = 10.6 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 136.1, 136.0, 132.4, 129.8, 129.0, 128.9, 128.6, 125.5, 125.1, 124.5, 21.4; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{12}N_3O_2$ 230.0930; found 230.0917.

(Z)−4−Bromo−1−styryl−1H−pyrazole ***(3n).*** The product was obtained as a yellow liquid (83.9 mg, 68% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.29–7.21 (m, 4H) 7.13–7.11 (m, 2H), 6.84 (d, J = 9.6 Hz, 1H), 6.22 (d, J = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 133.7, 129.4, 128.8, 128.5, 128.2, 126.5, 119.8, 94.6; HRMS (ESI–TOF) *m/z*: $(M+H)^+$Calcd for $C_{11}H_{10}BrN_2$ 249.0027; found 249.0051.

(Z)−5−Methyl−1−(4−(trifluoromethoxy)styryl)−1H−pyrazol−3−amine ***(3o).*** The product was obtained as a yellow semi–solid (101.8 mg, 72% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 9.5 Hz, 2H), 7.07 (d, J = 8.3 Hz, 2H), 6.60 (d, J = 9.1 Hz, 1H), 6.18 (d, J = 9.1 Hz, 1H), 5.48 (s, 1H), 3.70 (br s, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 148.3, 140.8, 133.2, 130.5, 124.1, 121.7, 121.3, 120.4, 95.0, 11.3; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{13}F_3N_3O$ 284.1011; found 284.1006.

(Z)−3,5−Dimethyl−1−(4−methylstyryl)−1H−pyrazole ***(3p).*** The product was obtained as a yellow semi–solid (68.9 mg, 65% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 7.6 Hz, 2H), 6.66 (d, J = 9.1 Hz, 1H), 6.40 (d, J = 9.1 Hz, 1H), 5.83 (s, 1H), 2.26 (s,

6H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 139.8, 138.0, 131.1, 129.0, 128.5, 127.7, 123.8, 105.7, 21.2, 13.6, 11.1; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{14}H_{15}N_2$ 213.1392; found 213.1376.

General procedure for the synthesis of (*E*)−styryl pyrazoles (4a–g): In an oven dried pressure tube, to a solution of pyrazoles **1a** and **1i–j** (0.5 mmol) in DMSO, finely crushed KOH (2.0 equiv) and alkynes **2a–b, 2n–2p** and **2q** (1.0 mmol) were added under inert atmosphere. The resulting reaction mixture was heated at 120 °C for 24 h. Progression of the reaction was monitored by TLC, while noticing complete consumption of alkynes, reaction was brought to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel mesh size 100–200 (hexane).

(E)−1−Styryl−1H−pyrazole ***(4a).*** The product was obtained as a yellow semi–solid (57.8 mg, 68% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.59 (m, 2H), 7.44 (d, J = 14.5 Hz, 1H), 7.36–7.34 (m, 2H), 7.27 (t, J = 7.6 Hz, 2H), 7.20–7.16 (m, 1H), 6.97 (d, J = 14.5 Hz, 1H), 6.33–6.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 134.9, 128.8, 128.0, 127.5, 126.3, 126.1, 116.9, 107.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_{11}N_2$ 171.0922; found 171.0915.

(E)−1−(4−Methylstyryl)−1H−pyrazole ***(4b).*** The product was obtained as a yellow semi–solid (64.4 mg, 70% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.58 (m, 2H), 7.41 (d, J = 14.5 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 7.6 Hz, 2H), 6.95 (d, J = 14.5 Hz, 1H), 6.32–6.31 (m, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 137.5, 132.1, 129.5, 127.8, 126.1, 125.7, 116.9, 107.1, 21.2; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{13}N_2$ 185.1079; found 185.1080.

(E)−1−(4−Bromostyryl)−1H−pyrazole ***(4c).*** The product was obtained as a yellow semi–solid (80.2 mg, 65% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 1.5 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.50–7.47 (m, 2H), 7.44 (s, 1H), 7.27 (d, J = 8.3 Hz, 2H), 6.99 (d, J = 14.5 Hz, 1H), 6.40–6.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 134.0, 131.9, 128.1, 127.6, 126.7, 121.2, 115.7, 107.5; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_{10}BrN_2$ 249.0027; found 249.0051.

(E)−1−(3,5−Dimethoxystyryl)−1H−pyrazole ***(4d).*** The product was obtained as a yellow oil (78.2 mg, 68% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 1H), 7.51 (s, 1H), 7.43 (d, J = 14.5 Hz, 1H), 7.30–7.29 (m, 1H), 6.51–6.50 (m, 1H), 6.32–6.30 (m, 1H), 6.269–6.263 (m, 1H), 6.14–6.12 (m, 1H), 3.73 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 140.3, 136.1, 129.8, 127.2, 119.1, 106.3, 104.2, 100.3, 55.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{15}N_2O_2$ 231.1134; found 231.1135.

(E)−1−(2−(Phenanthren−9−yl)vinyl)−1H−pyrazole ***(4e)***. The product was obtained as orange needles (89.1 mg, 66% yield), mp 91–94 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 7.7 Hz, 1H), 8.58 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 7.7 Hz, 1H), 7.81–7.78 (m, 2H), 7.72 (d, J = 13.7 Hz, 1H), 7.666–7.660 (m, 2H), 7.63–7.61 (m, 1H), 7.59–7.58 (m, 1H), 7.56 (s, 1H), 7.54–7.51 (m, 1H), 7.48 (d, J = 14.2 Hz, 1H), 6.37–6.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 131.7, 131.4, 130.7, 130.4, 130.3, 128.6, 128.4, 126.9, 126.8, 126.73, 126.66, 124.8, 124.5, 123.1, 122.5, 114.8, 107.4; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{19}H_{15}N_2$ 271.1235; found 271.1231.

(E)−4−Bromo−1−(4−(trifluoromethyl)styryl)−1H−pyrazole ***(4f).*** The product was obtained as a yellow solid (100.8 mg, 64% yield), mp: 90–92 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s,

1H), 7.56 (s, 1H), 7.53–7.51 (m, 2H), 7.42 (s, 1H), 7.41–7.40 (m, 1H), 7.38 (s, 1H), 6.94 (d, *J* = 14.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 138.2, 129.8, 129.5, 128.1, 127.6, 126.4, 125.8 (q, *J* = 3.8 Hz, 1C), 116.1, 95.9; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_9BrF_3N_2$ 316.9901; found 316.9897.

(E)−4−Bromo−3,5−dimethyl−1−(4−(trifluoromethyl)styryl)−1H−pyrazole ***(4g).*** The product was obtained as a yellow semi–solid (106.6 mg, 62% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 13.7 Hz, 1H), 7.15 (d, *J* = 13.4 Hz, 1H), 2.30 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 139.0, 137.6, 128.1, 127.6, 126.2, 125.7 (q, *J* = 3.9 Hz, 1C), 124.3, 115.7, 97.0, 12.5, 10.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{14}H_{13}BrF_3N_2$ 345.0214; found 345.0224.

(E)-1-(4-(Trifluoromethyl)styryl)-1H-pyrazole ***(4h).*** The product was obtained as a white solid (53.75 mg, 45% yield), mp: 100–102 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.67 (m, 2H), 7.60–7.58 (m, 2H), 7.55–7.49 (m, 3H), 7.08 (d, *J* = 14.2 Hz, 1H), 6.42 (t, *J* = 1.83 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 138.7, 129.4, 129.1, 128.4, 128.0, 126.2, 125.80–125.70 (m, 1C), 122.8, 115.3, 107.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{10}F_3N_2$ 239.0796; found 239.0794.

(E)-1-(4-Nitrostyryl)-1H-pyrazole ***(4i).*** The product was obtained as a dark yellow solid (53.55 mg, 50% yield), mp: 190–192 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.20 (m, 2H), 7.718–7.714 (m, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.64 (d, *J* = 14.2 Hz, 1H), 7.56–7.54 (m, 2H), 7.12 (d, *J* = 14.6 Hz, 1H), 6.45 (t, *J* = 1.83 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 142.2, 142.0, 129.4, 128.8, 126.5, 124.3, 114.5, 108.2; HRMS (EI-TOF) *m/z*: $(M)^+$Calcd for $C_{11}H_9N_3O_2$ 215.0676; found 215.0676.

General procedure for the synthesis of *N*− styryl pyrazoles (5a–m): In an oven dried pressure tube, to a solution of pyrazoles **1a, 1d and 1f** (0.5 mmol) in DMSO, finely crushed KOH (1.0 equiv) and alkynes **2aa**–**2ak** (1.0 mmol) were added under inert atmosphere. The resulting reaction mixture was heated at 120 °C for 4−5 h. Progression of the reaction was monitored by TLC, while noticing complete consumption of alkynes, reaction was brought to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel mesh size 100–200 (hexane).

(Z)−1−(3−Phenylprop−1−en−1−yl)−1H−pyrazole ***(5a).*** The product was obtained as a pale yellow oil (57.0 mg, 62% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.72 (m, 1H), 7.65 (s, 1H), 7.37–7.31 (m, 5H), 7.25–7.22 (m, 1H), 7.06 (s, 1H), 6.36–6.35 (m, 1H), 2.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 135.8, 135.5, 129.0, 128.2, 126.8, 126.7, 117.0, 106.5, 15.6 ; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{13}N_2$ 185.1079; found 185.1096.

(Z)−1−(4−Phenylbut−1−en−1−yl)−1H−pyrazole ***(5b).*** The product was obtained as a reddish oil (59.4 mg, 60% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.38–7.36 (m, 1H), 7.31–7.28 (m, 3H), 7.27–7.25 (m, 1H), 7.22–7.21 (m, 1H), 6.42–6.38 (m, 1H), 6.23–6.22 (m, 1H), 6.14–6.07 (m, 1H), 4.25 (t, J = 7.2 Hz, 2H), 2.78 (q, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 137.1, 132.7, 129.1, 128.5, 127.3, 126.1, 125.6, 105.3, 51.9, 34.0; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{15}N_2$ 199.1235; found 199.1230.

(Z)−3−(1H−pyrazol−1−yl)prop−2−en−1−ol ***(5c).*** The product was obtained as a yellow oil (42.1 mg, 68% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.72 (m, 1H), 7.536–7.532 (m, 1H), 6.29–6.28 (m, 1H), 5.22 (s, 1H), 4.86 (m, 1H), 4.48–4.47 (m, 2H), 4.30 (br s, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 141.5, 130.7, 127.4, 117.4, 106.8, 56.8; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_6H_9N_2O$ 125.0715; found 125.0716.

(Z)−6−(1H−Pyrazol−1−yl)hex−5−en−1−ol ***(5d).*** The product was obtained as a green oil (48.1 mg, 58% yield), ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.61 (m, 2H), 6.349–6.345 (m, 1H), 5.25 (s, 1H), 4.74 (s, 1H), 3.74–3.67 (m, 3H), 2.72–2.69 (m, 2H), 1.77–1.73 (m, 2H), 1.33–1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 140.3, 127.1, 116.8, 106.8, 62.3, 32.2, 31.7, 23.6; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_9H_{15}N_2O$ 167.1184; found 167.1182.

(Z)−1−(2−(1H−Pyrazol−1−yl)vinyl)cyclopentanol ***(5e)***. The product was obtained as a brown oil (48.9 mg, 55% yield), ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.41 (s, 1H), 6.92 (s, 1H), 6.54 (d, J = 10.6 Hz, 1H), 6.27 (s, 1H), 5.39 (d, J = 10.6 Hz, 1H), 2.00–1.96 (m, 2H), 1.83 (s, 2H), 1.59–1.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 131.2, 125.6, 123.7, 106.5, 78.5, 41.3, 23.5; HRMS (ESI–TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{10}H_{14}N_2ONa$ 201.1004; found 201.0980.

(Z)−1−(2−(1H−Pyrazol−1−yl)vinyl)cyclohexanol ***(5f).*** The product was obtained as a brown oil (57.6 mg, 60% yield), ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.417–7.412 (m, 1H), 7.14 (s, 1H), 6.52 (d, J = 10.6 Hz, 1H), 6.26–6.25 (m, 1H), 5.25 (d, J = 10.6 Hz, 1H), 1.73–1.63 (m, 4H), 1.66–1.55 (m, 2H), 1.41–1.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 131.3, 125.8, 123.0, 106.5, 69.4, 38.4, 25.6, 22.3; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_{17}N_2O$ 193.1341; found 193.1336.

(Z)−1−(3−Methoxyprop−1−en−1−yl)−1H−pyrazole ***(5g)***. The product was obtained as a yellow oil (46.9 mg, 68% yield), ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.53–7.52 (m, 1H), 6.82–6.79 (m, 1H), 6.33–6.32 (m, 1H), 5.37–5.35 (m, 1H), 4.44 (d, J = 6.1 Hz, 2H), 3.38 (m,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 130.3, 126.3, 116.3, 106.6, 68.6, 58.3; HRMS (ESI$^-$TOF) *m/z*: $(M+H)^+$ Calcd for $C_7H_{11}N_2O$ 139.0871; found 139.0879.

(Z)−1−(3−Phenoxyprop−1−en−1−yl)−1H−pyrazole ***(5h).*** The product was obtained as a yellow oil (60.0 mg, 60% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.55 (m, 1H), 7.53–7.52 (m, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.23 (t, *J* = 8.3 Hz, 1H), 7.15–7.10 (m, 2H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.92–6.87 (m, 2H), 6.29–6.21 (m, 1H), 4.62–4.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 140.1, 134.5, 129.6, 122.9, 120.7, 116.1, 114.7, 106.1, 64.4; HRMS (ESI$^-$TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{13}N_2O$ 201.1028; found 201.1054.

(Z)−3−(3−(Trifluoromethyl)−1H−pyrazol−1−yl)prop−2−en−1−ol ***(5i).*** The product was obtained as a brown oil (66.2 mg, 69% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.52 (m, 1H), 6.74 (d, *J* = 9.9 Hz, 1H), 6.56–6.55 (m, 1H), 5.67–5.61 (m, 1H), 4.34 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 144.0, 131.9, 126.4, 121.1, 105.3, 57.1; HRMS (ESI$^-$TOF) *m/z*: $(M+Na)^+$ Calcd for $C_7H_7F_3N_2ONa$ 215.0408; found 215.0417.

(Z)−1−(4−Phenylbut−1−en−1−yl)−3−(trifluoromethyl)−1H−pyrazole ***(5j)***. The product was obtained as a pale white oil (78.4 mg, 59% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.19–7.16 (m, 2H), 7.13–7.11 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.36 (s, 1H), 6.05 (q, *J* = 21.3 Hz, 1H), 3.95 (s, 2H), 1.86 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 137.1, 129.2, 128.7, 128.5, 128.0, 126.7, 122.6, 117.9, 104.4, 34.1, 29.7; HRMS (ESI$^-$TOF) *m/z*: $(M+H)^+$ Calcd for $C_{14}H_{14}F_3N_2$ 267.1109; found 267.1113.

(Z)−4−Bromo−1−(hex−1−en−1−yl)−1H−pyrazole ***(5k).*** The product was obtained as a yellow oil (45.6 mg, 40% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.48 (s, 1H), 5.18 (s, 1H), 4.67 (s, 1H), 2.53 (t, *J* = 7.6 Hz, 2H), 1.47–1.39 (m, 2H), 1.35–1.26 (m, 2H), 0.85 (t, *J* = 7.6 Hz,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 140.6, 127.1, 100.5, 94.6, 32.0, 29.3, 22.2, 13.8; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_9H_{14}BrN_2$ 229.0340; found 229.0326.

(Z)−5−(4−Bromo−1H−pyrazol−1−yl)pent−4−en−1−ol ***(5l).*** The product was obtained as a brown semi–solid (69.0 mg, 60% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.56 (s, 1H), 5.24 (s, 1H), 4.80 (s, 1H), 3.67 (t, *J* = 6.1 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 1.84–1.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 140.7, 134.3, 127.3, 100.9, 62.1, 31.7, 23.5; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_8H_{12}BrN_2O$ 231.0133; found 231.0130.

(E)−Ethyl 3−(1H−pyrazol−1−yl)acrylate ***(5m).*** The product was obtained as a light brown semi–solid (54.7 mg, 66% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 13.7 Hz, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 6.40–6.39 (m, 1H), 6.31 (d, *J* = 13.7 Hz, 1H), 4.21 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 143.4, 139.5, 130.0, 109.0, 105.7, 60.5, 14.2; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_8H_{11}N_2O_2$ 167.0821; found 167.0842.

General procedure for the synthesis of *N*− styryl pyrazoles (7a–k): In an oven dried pressure tube, to a solution of pyrazoles **1a–b, 1d** and **1f** (0.5 mmol) in DMSO, finely crushed KOH (1.5 equiv) and alkynes **6a–h** (0.5 mmol) were added under inert atmosphere. The resulting reaction mixture was heated at 120 °C for 24 h. Progression of the reaction was monitored by TLC, while noticing complete consumption of alkynes, reaction was brought to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel mesh size 100–200 (hexane).

(Z)−1−(1,2−Diphenylvinyl)−1H−pyrazole ***(7a).*** The product was obtained as a yellow semi−solid (86.1 mg, 70% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.697–7.694 (m, 1H), 7.30–7.29 (m, 1H), 7.28–7.25 (m, 3H), 7.16–7.15 (m, 1H), 7.14–7.13 (m, 2H), 7.12–7.11 (m, 2H), 6.94 (s, 1H), 6.75–6.72 (m, 2H), 6.32–6.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 138.0, 137.4, 134.0, 131.5, 128.7, 128.6, 128.4, 128.2, 127.8, 125.9, 124.6, 106.6; HRMS (ESI−TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{17}H_{14}N_2Na$ 269.1055; found 269.1048.

(Z)−1−(1,2−Di−p−tolylvinyl)−1H−pyrazole ***(7b).*** The product was obtained as a pale white oil (93.1 mg, 68% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.37–7.36 (m, 1H), 7.14–7.08 (m, 4H), 6.99 (d, J = 7.7 Hz, 2H), 6.93 (s, 1H), 6.67 (d, J = 8.2 Hz, 2H), 6.38–6.37 (m, 1H), 2.34 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 138.7, 137.9, 137.4, 135.0, 131.6, 131.5, 129.2, 129.1, 128.7, 125.9, 124.0, 106.7, 21.2; HRMS (ESI−TOF) *m/z*: $(M+H)^+$ Calcd for $C_{19}H_{19}N_2$ 275.1548; found 275.1545.

(Z)−1−(2−(m−Tolyl)−1−(p−tolyl)vinyl)−1H−pyrazole ***(7c).*** The product was obtained as a pale yellow oil (89.0 mg, 65% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.76 (m, 1H), 7.16–7.12 (m, 3H), 7.10–7.05 (m, 1H),7.01–6.97 (m, 3H), 6.94–6.92 (m, 1H), 6.68 (d, J = 8.7 Hz, 1H), 6.60–6.57 (m, 1H), 6.40–6.38 (m, 1H), 2.28 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 138.9, 134.9, 134.2, 131.5, 129.6, 129.3, 128.7, 128.2, 126.0, 125.8, 124.9, 124.1, 123.2, 106.6, 21.3, 21.2; HRMS (ESI−TOF) *m/z*: $(M+H)^+$ Calcd for $C_{19}H_{19}N_2$ 275.1548; found 275.1545.

(Z)−1−(2−(4−Bromophenyl)−1−(p−tolyl)vinyl)−1H−pyrazole ***(7d).*** The product was obtained as yellow semi−solid (119.9 mg, 71% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.67 (m, 1H), 7.29–7.22 (m, 3H), 7.09–7.02 (m, 4H), 6.80 (s, 1H), 6.56 (d, J = 8.3 Hz, 2H), 6.33–6.32 (m, 1H),

2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 138.8, 133.3, 131.7, 131.5, 130.2, 129.3, 129.2, 128.8, 127.5, 126.1, 122.5, 121.8, 107.0, 21.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{18}H_{16}BrN_2$ 339.0497; found 339.0495.

(Z)−1−(2−(4−Nitrophenyl)−1−phenylvinyl)−1H−pyrazole ***(7e).*** The product was obtained as yellow solid (101.8 mg, 70% yield), mp: 120−122 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 2H), 7.72 (s, 1H), 7.51–7.42 (m, 3H), 7.37 (s, 1H), 7.33–7.31 (m, 2H), 7.21 (d, J = 2.2 Hz, 1H), 7.07 (d, J = 9.1 Hz, 2H), 6.33–6.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 142.4, 141.7, 141.2, 133.2, 130.3, 130.2, 129.64, 129.58, 129.5, 123.4, 116.0, 107.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{14}N_3O_2$ 292.1086; found 292.1079.

(Z)−1−(1,2−Di(thiophen−3−yl)vinyl)−1H−pyrazole ***(7f).*** The product was obtained as a dark brown semi-solid (79.9 mg, 62% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.78 (m, 1H), 7.45–7.44 (m, 1H), 7.29–7.27 (m, 1H), 7.16–7.14 (m, 1H), 7.10–7.08 (m, 1H), 7.06 (s, 1H), 6.82 (dd, J = 12.2 and 1.5 Hz, 2H), 6.45–6.44 (m, 1H), 6.13 (d, J = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 139.9, 135.0, 132.6, 131.0, 127.1, 126.5, 125.7, 125.5, 124.5, 122.4, 119.3, 106.8; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{11}N_2S_2$ 259.0364; found 259.0362.

(Z)−1−(1−Phenylprop−1−en−2−yl)−1H−pyrazole ***(7g).*** The product was obtained as a yellow liquid (66.2 mg, 72% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.71 (m, 1H), 7.66 (s, 1H), 7.37–7.31 (m, 4H), 7.25–7.24 (m, 1H), 7.08 (s, 1H), 6.36–6.35 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 135.8, 135.5, 129.0, 128.2, 126.8, 126.7, 116.9, 106.5, 15.6; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{13}N_2$ 185.1079; found 185.1074.

(Z)−3−Phenyl−2−(1H−pyrazol−1−yl)prop−2−en−1−ol ***(7h).*** The product was obtained as a yellow liquid (65.0 mg, 65% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.57 (m, 1H), 7.479–

7.473 (m, 1H), 7.10–7.09 (m, 2H), 6.77–6.74 (m, 2H), 6.51 (s, 1H), 6.32 (br s, 1H), 6.21 (t, *J* = 3.8 Hz, 1H), 6.16–6.15 (m, 1H), 4.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 137.8, 133.6, 131.0, 128.5, 127.8, 122.4, 106.4, 104.8, 64.5; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{13}N_2O$ 201.1028; found 201.1022.

(Z)−3−Methyl−1−(1−phenylprop−1−en−2−yl)−1H−pyrazole ***(7i).*** The product was obtained as a pale/light yellow semi-solid (68.3 mg, 69% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.557–7.553 (m, 1H), 7.29–7.23 (m, 4H), 7.18–7.16 (m, 1H), 6.97 (s, 1H), 6.09–6.08 (m, 1H), 2.31 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 136.2, 135.3, 129.1, 128.2, 127.6, 126.6, 116.0, 106.5, 15.6, 13.8; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{15}N_2$ 199.1235; found 199.1204.

(Z)−1−(1,2−Diphenylvinyl)−3−(trifluoromethyl)−1H−pyrazole ***(7j).*** The product was obtained as a white oil (102.0 mg, 65% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 4H), 7.17–7.12 (m, 5H), 7.04 (s, 1H), 6.74–6.72 (m, 2H), 6.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 136.6, 133.6, 133.5, 132.4, 131.6, 130.1, 129.3, 128.8, 128.7, 128.61, 128.55, 128.3, 126.3, 125.9, 105.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{18}H_{14}F_3N_2$ 315.1109; found 315.1111.

(Z)−4−Bromo−1−(1,2−diphenylvinyl)−1H−pyrazole ***(7k).*** The product was obtained as a pale/light yellow semi-solid (102.0 mg, 63% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.33 (s, 1H), 7.31–7.28 (m, 3H), 7.18–7.14 (m, 5H), 6.93 (s, 1H), 6.79–6.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 137.6, 137.0, 133.8, 131.7, 129.2, 128.8, 128.7, 128.6, 128.4, 126.1, 125.3, 94.5; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{17}H_{13}BrN_2Na$ 347.0160; found 347.0147.

General procedure for the synthesis of *N*− styryl benzpyrazoles (8a–g): In an oven dried pressure tube, to a solution of pyrazoles **1k–l** (0.5 mmol) in DMSO, finely crushed KOH (1.0 equiv) and alkynes **2a–c, 2h, 2n** and **6a** (1.0 mmol) were added under inert atmosphere. The resulting reaction mixture was heated at 120 °C for 8−36 h. Progression of the reaction was monitored by TLC, while noticing complete consumption of alkynes, reaction was brought to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel mesh size 100–200 (hexane).

(Z)−5−Bromo−1−styryl−1H−indazole ***(8a).*** The product was obtained as a yellow oil (96.8 mg, 65% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.05 (m, 1H), 7.838–7.832 (m, 1H), 7.248–7.244 (m, 1H), 7.15–7.13 (m, 3H), 7.05 (d, J = 9.7 Hz, 1H), 7.02–7.00 (m, 2H), 6.85 (d, J = 9.1 Hz, 1H), 6.48 (d, J = 9.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 136.4, 134.8, 134.1, 129.8, 128.8, 128.3, 128.1, 123.74, 123.67, 123.3, 114.6, 112.4; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{12}BrN_2$ 299.0184; found 299.0210

(Z)−5−Bromo−1−(4−methylstyryl)−1H−indazole ***(8b).*** The product was obtained as a yellow semi-solid (98.2 mg, 63%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.78 (s, 1H), 7.23–7.21 (m, 1H), 6.94 (d, J = 9.1 Hz, 1H), 6.90–6.88 (m, 2H), 6.85–6.83 (m, 3H), 6.41 (d, J = 9.1 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 140.8, 139.3, 134.7, 129.8, 129.0, 128.7, 128.4, 124.2, 123.3, 123.0, 118.1, 112.4, 21.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{16}H_{14}BrN_2$ 313.0340; found 313.0338.

(Z)−5−Bromo−1−(4−bromostyryl)−1H−indazole ***(8c).*** The product was obtained as a dark brown semi-solid (125.6 mg, 67% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.71 (s, 1H), 7.58 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.35–7.33 (m, 1H), 7.22 (d, J = 9.9 Hz,

1H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.49 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 135.8, 133.4, 133.1, 131.4, 130.5, 130.3, 125.4, 123.5, 122.2, 121.64, 121.58, 113.5; HRMS (EI-TOF) *m/z*: $(M)^+$ Calcd for $C_{15}H_{10}Br_2N_2$ 375.9211; found 375.9217.

(Z)−5−Bromo−1−(2−(thiophen−3−yl)vinyl)−1H−indazole ***(8d).*** The product was obtained as a brown semi-solid (90.9 mg, 60% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.82–7.81 (m, 1H), 7.30 (dd, *J* = 9.1 and 1.8 Hz, 1H), 7.15–7.14 (m, 1H), 7.03–7.01 (m, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.56–6.53 (m, 1H), 6.48 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 134.9, 134.6, 130.0, 128.0, 126.0, 125.7, 125.3, 123.4, 122.1, 119.1, 114.7, 112.1; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{10}BrN_2S$ 304.9748; found 304.9737.

(Z)−6−Bromo−1−styryl−1H−indole ***(8e).*** The product was obtained as a dark brown semi-solid (92.3 mg, 62% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.81 (m, 1H), 7.73 (s, 1H), 7.43 (d, *J* = 4.8 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.22–7.21 (m, 2H), 7.14–7.10 (m, 1H), 7.08–7.02 (m, 3H), 6.50 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 138.8, 133.5, 128.8, 128.6, 127.1, 126.7, 126.2, 124.0, 123.9, 121.8, 120.0, 117.8; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{12}BrN_2$ 299.0184; found 299.0203.

(Z)−6−Bromo−1−(4−ethylstyryl)−1H−indazole ***(8f).*** The product was obtained as a dark brown semi-solid (97.8 mg, 60% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 11.4 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.15–7.09 (m, 4H), 7.05–7.03 (m, 2H), 6.53 (d, *J* = 9.1 Hz, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 144.9, 130.6, 128.6, 128.3, 126.4, 126.1, 124.4, 123.9, 121.8, 120.8, 120.3, 120.0, 28.6, 15.3; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{16}BrN_2$ 327.0497; found 327.0491.

(Z)−6−Bromo−1−(1,2−diphenylvinyl)−1H−indazole ***(8g).*** The product was obtained as a dark brown semi-solid (114.0 mg, 61% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.86 (d, J = 26.7 Hz, 1H), 7.51 (d, J = 9.1 Hz, 1H), 7.24–7.22 (m, 4H), 7.13–7.06 (m, 4H), 7.00–6.98 (m, 2H), 6.68–6.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 137.4, 135.8, 135.7, 134.2, 129.0, 128.7, 128.5, 128.4, 128.2, 126.5, 126.1, 125.0, 123.1, 122.0, 121.3, 113.6; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{21}H_{16}BrN_2$ 375.0497; found 375.0479.

General procedure for the synthesis of bis-hydroaminated-heterocycles (9a−e): In an oven dried pressure tube, to a solution of *N*−heterocycles **1a, 1l** and **1m**–**o** (0.5 mmol) each in DMSO, finely crushed KOH (1.0 equiv) and alkynes **2r**–**s** (0.25 mmol) were added under inert atmosphere. The resulting reaction mixture was heated at 120 °C for 0.5 h-2 h. Progression of the reaction was monitored by TLC, while noticing complete consumption of alkynes, reaction was brought to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel mesh size 100–200 (hexane).

1,3−Bis((Z)−2−(4−iodo−1H−pyrazol−1−yl)vinyl)benzene ***(9a).*** The product was obtained as a yellow oil (148.7 mg, 58%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 2H), 7.26 (s, 2H), 7.18 (d, J = 7.6 Hz, 1H), 7.01 (d, J = 7.6 Hz, 2H), 6.94 (s, 1H), 6.83 (d, J = 9.9 Hz, 2H), 6.12 (d, J = 9.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 134.2, 133.6, 132.3, 129.0, 128.2, 126.4, 119.8, 119.5, 58.2; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{16}H_{13}I_2N_4$ 514.9230; found 514.9233.

1,4−Bis((Z)−2−(6−bromo−1H−indazol−1−yl)vinyl)benzene ***(9b).*** The product was obtained as a yellow solid (116.3 mg, 45%), mp: 100−101 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 2H), 7.69 (s, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.30–7.27 (m, 3H), 7.22 (d, J = 6.8 Hz, 3H), 6.92 (s, 2H),

6.86 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 134.9, 133.3, 128.8, 125.0, 124.7, 122.5, 122.0, 121.3, 117.9, 117.0, 112.7; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{24}H_{17}Br_2N_4$ 518.9820; found 518.9812.

1−((Z)−3−((Z)−2−(1H−pyrazol−1−yl)vinyl)styryl)−1H−1,2,4−triazole ***(9c).*** The product was obtained as a yellow oil (77.5 mg, 59%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 10.3 Hz, 2H), 7.53 (s, 1H), 7.24–7.14 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.97–6.93 (m, 3H), 6.88 (dd, *J* = 9.1 and 2.2 Hz, 1H), 6.42 (d, *J* = 9.9 Hz, 1H), 6.16–6.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 140.3, 135.1, 133.5, 129.4, 129.3, 129.0, 128.7, 127.4, 127.1, 123.6, 123.3, 118.2, 106.7; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{14}N_5$ 264.1249; found 264.1242.

1−((Z)−4−((Z)−2−(1H−Pyrazol−1−yl)vinyl)styryl)−1H−indole ***(9d).*** The product was obtained as a white solid (91.7 mg, 59%), mp: 100−101 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.51 (m, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.35–7.31 (m, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.25–7.22 (m, 1H), 7.20–7.15 (m, 2H), 7.11–7.09 (m, 2H), 7.06–7.04 (m, 3H), 6.96 (d, *J* = 11.4 Hz, 2H), 6.53–6.51 (m, 1H), 6.27–6.24 (m, 1H), 6.20–6.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 140.4, 135.6, 134.5, 133.4, 129.5, 129.1, 128.8, 128.5, 126.9, 126.1, 123.7, 122.4, 120.9, 120.7, 119.2, 118.9, 116.3, 110.2, 106.7, 104.1; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{21}H_{18}N_3$ 312.1501; found 312.1498.

(Z)−1−(2,4−Bis(4−methoxyphenyl)but−1−en−3−yn−1−yl)−1H−pyrazole ***(9e).*** The product was obtained as a yellow semi–solid (79.2 mg, 48% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–8.16 (m, 1H), 7.727–7.723 (m, 1H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 6.46 (t, *J* = 2.2 Hz, 1H), 5.97 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 159.7, 146.5, 140.7, 132.9, 132.1, 128.74, 128.68,

115.2, 114.0, 113.9, 105.8, 99.3, 95.3, 84.9, 55.34, 55.26; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{21}H_{19}N_2O_2$ 331.1447; found 331.1447.

General procedure for the synthesis of deuteurated *N*− styryl pyrazoles (10a–e & 10h): In an oven dried pressure tube, to a solution of pyrazoles **1a** (0.5 mmol) in DMSO−d_6, finely crushed KOH (0.5–2.0 equiv) and alkynes **2b, 2ac** and **6b** (1.0 mmol) were added under inert atmosphere. The resulting reaction mixture was heated at 120 °C for 0.5 h–24 h. Progression of the reaction was monitored by TLC, while noticing complete consumption of alkynes, reaction was brought to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel mesh size 100–200 (hexane).

(Z)−1−Styryl−1H−pyrazole ***(10a).*** The product was obtained as a yellow semi–solid (60.2 mg, 70% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.58 (m, 1H), 7.31–7.24 (m, 4H), 7.20–7.18 (m, 2H), 6.18–6.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 134.0, 129.1, 128.3, 128.2, 127.5, 126.6–126.5 (m, 1C), 118.6–118.3 (m, 1C), 106.3; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_9D_2N_2$ 173.1048; found 173.1037.

(Z)−1−(4−Methylstyryl)−1D−pyrazole ***(10b).*** The product was obtained as a orange semi–solid (63.2 mg, 68% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.347–7.341 (m, 1H), 7.11–7.06 (m, 4H), 6.20–6.19 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 137.7, 131.2, 128.6, 128.5, 128.4, 126.4–126.0 (m, 1C), 119.2–118.6 (m, 1C), 106.5, 21.2; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{11}D_2N_2$ 187.1204; found 187.1200.

(Z)−3−(1D−Pyrazol−1−yl)prop−2−en−1−ol ***(10c).*** The product was obtained as a yellow semi–solid (39.3 mg, 62% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 6.30–6.29 (m,

1H), 4.49–4.48 (m, 2H), 3.61 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1–143.7 (m, 1C), 140.5, 126.8–126.7 (m, 1C), 107.0, 99.1–98.9 (m, 1C), 63.3; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_6H_7D_2N_2O$ 127.0840; found 127.0835.

(Z)−1−(1,2−Di−p−tolylvinyl)−1D−pyrazole (***10d***)**.** The product was obtained as a pale white semi–solid (82.8 mg, 60% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.37 (s, 1H), 7.15–7.08 (m, 4H), 7.00 (d, J = 8.3 Hz, 2H), 6.67 (d, J = 8.3 Hz, 2H), 2.34 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 138.7, 137.9, 137.3, 135.0, 131.4, 129.4, 129.2, 128.7, 126.0, 125.8, 124.1–123.3 (m, 1C), 106.9–106.4 (m, 1C), 21.3, 21.2; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{19}H_{18}DN_2$ 276.1611; found 276.1612.

(Z)−1−Styryl−1H−pyrazole (***10e***)**.** The product was obtained as a orange semi–solid (56.2 mg, 65% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.608–7.601 (m, 1H), 7.37–7.35 (m, 2H), 7.30–7.26 (m, 2H), 7.21–7.17 (m, 1H), 6.339–6.332 (m, 0.85H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0–140.8 (m, 1C), 134.8, 128.7, 128.5–128.4 (m, 1C), 127.4, 127.1–127.0 (m, 1C), 126.0, 116.6–116.4 (m, 1C), 107.0–106.9 (m, 1C); HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_8D_3N_2$ 174.1111; found 174.1110.

(Z)−1−Styryl−1H−pyrazole (***10h***)**.** The product was obtained as a brown semi–solid (48.1 mg, 55% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.7 Hz, 2H), 7.48–7.44 (m, 2H), 7.38–7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1–141.0 (m, 1C), 135.0, 128.8, 127.9–127.8 (m, 1C), 127.5, 126.4–126.3 (m, 1C), 126.1, 116.9–116.6 (m, 1C), 107.3–107.1 (m, 1C), 106.3; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_6D_5N_2$ 176.1236; found 176.1217.

1-Phenethyl-1H-pyrazole (***11a***)**.** The product was obtained as a light brown semi–solid (55.9 mg, 65%) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.526–7.522 (m, 1H), 7.27–7.19 (m, 3H), 7.13 (d, J = 2.2

Hz, 1H), 7.06 (d, *J* = 6.8 Hz, 2H), 6.15 (t, *J* = 2.2 Hz, 1H), 4.32 (t, *J* = 7.6 Hz, 2H), 3.14 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 138.0, 129.2. 128.6, 128.4, 126.5, 104.9, 55.4, 36.8; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_{13}N_2$ 173.1079; found 173.1077.

(Z)-5-Bromo-1-(4-(p-tolylethynyl)styryl)-1H-indazole (***11b***)**.** The product was obtained as a brown solid (144.2 mg, 70%), mp: 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 8.7 Hz, 1H), 7.36–7.30 (m, 3H), 7.28–7.24 (m, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 7.02–6.98 (m, 2H), 6.28 (d, *J* = 9.1 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.7, 135.7, 133.3, 131.9, 131.5, 131.3, 130.7, 129.22, 129.16, 127.5, 125.3, 123.7, 123.4, 122.3, 121.8, 121.9, 119.8, 113.3, 90.4, 88.8, 21.5; HRMS (ESI–TOF) *m/z*: $(M+H)^+$ Calcd for $C_{24}H_{18}BrN_2$ 413.0653; found 413.0674.

Acknowledgement: The Research work was supported by Council of Scientific and Industrial Research (CSIR) and University of Delhi. V.G and P.B are thankful to CSIR and UGC for fellowship, respectively.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR and HRMS spectra for compounds are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

References

1. Recent Reviews: (a) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. *Org. Biomol. Chem*. **2016**, *14*, 6611. (b) Ponra, S.; Majumdar, K. C. *RSC Adv*. **2016**, 6, 37784. (c) Sadjadi, S.; Heravi, M. M.; Nazari, N. *RSC Adv*. **2016**, *6*, 53203. (d) Chen, Z. P.; Zhou, Y. G. *Synthesis* **2016**, *48*, 1769. (e) Rohokale, R. S.; Kshirsagar, U. A. *Synthesis* **2016**, *48*, 1253. (f) Ye, Z. S.; Gettys, K. E.; Dai, M. J.

Beilstein. *J. Org. Chem*. **2016**, *12*, 702. (g) Kumari, S.; Kishore, D.; Paliwal, S.; Chauhan, R.; Dwivedi, J.; Mishra, A. *Mol. Diversity* **2016**, *20*, 185. (h) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. *Res. Chem. Intermed*. **2016**, *42*, 5147. (i) He, Q.; Yin, Z. Q.; Chen, H. B.; Zhang, Z. M.; Wang, X. X.; Yue, G. Z. *Prog. Chem*. **2016**, *28*, 801.

2. (a) Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol Rev* **2002**, *54*, 161.(b) Haydl, A. M.; Xu, K.; Breit, B. *Angew. Chem*. **2015**, *127*, 7255. (c) Bruno, O.; Brullo, C.; Bondavalli, F.; Schenone, S.; Ranise, A.; Arduino, N.; Bertolotto, M. B.; Montecucco, F.; Ottonello, L.; Dallegri, F.; Tognolini, M.; Ballabeni, V.; Bertoni, S.; Barocelli, E. *J. Med. Chem.* **2007,** *50*, 3618.
3. Selvam,T. P.; Kumar, P.V.; Saravanan, G.; Prakash, C. R. *Journal of Saudi Chemical Society* **2014,** *18*, 1015.
4. Çetin, A. *Int. J. Curr. Res. Chem. Pharma. Sci.* **2015**, *7*, 8.
5. Alegaon, S. G.; Alagawadi, K. R.; Dadwe, D. H. Drug Res. **2014,** *64*, 553.
6. Koca, I.; Ozgur, A.; Coskun, K. A.; Tutar, Y. *Bioorg. Med. Chem*. **2013,** *21*, 3859.
7. Tanitame, A.; Oyamada, Y.; Ofuji, K.; Terauchi, H.; Kawasaki, M.; Wachi, M.; Yamagishi, J. I. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 4299.
8. Tyagarajan, S.; Chakravarty, P. K.; Zhou, B.; Taylor, B.; Eid, R.; Fisher, M. H.; Parsons, W. H.; Wyvratt, M. J.; Lyons, K. A.; Klatt, T.; Li, X.; Kumar, S.; Williams, B.; Felix, J.; Priest, B. T.; Brochu, R. M.; Warren, V.; Smith, M.; Garcia, M.; Kaczorowski, G. J. *Bioorg. Med. Chem. Lett***. 2010**, *20*, 7479.
9. Shih, S. R.; Chu, T. Y.; Reddy, G.; Tseng, S. N.; Chen, H. L.; Tang, W. F.; Wu, M. S.; Yeh, J. Y.; Chao, Y. S.; Hsu, J.; Hsieh, H. P.; Horng, J. T. *J. Biomed. Sci*. **2010**, *17*, 13.

10. Bandgar, B. P.; Gawande, S. S.; Bodade, R. G.; Gawande, N. M.; Khobragade, C. N. *Bioorg. Med. Chem*. **2009**, *17*, 8168.

11. Bole, S. B.; Nargund, R.; Nargund, L. V. G.; Devaraju, K. S.; Vedamurthy, A. B.; Shruti, S. D.; *Der Pharma Chemica*, **2011,** *3* (5) 73.

12. Kelekci, G. N.; Koyunoglu, S.; Yabanoglu, S.; Yelekci, K.; Ozgen, O.; Ucar, G.; Erol, K.; Kendi, E.; Yesilada, A. *Bioorg. Med. Chem*. **2009**, *17*, 675.

13. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999,** *42,* 769.

14. Damljanovic, I.; Evic, M. V; Radulovic, N.; Palic, R.; Ellmerer, E.; Ratkovic, Z. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1093.

15. (a) Alegaon, S. G.; Hirpara, M. B.; Alagawadi, K. R.; Hullatti, K. K.; Kashniyal, K. *Bioorg. Med. Chem. Lett.* **2014,** *24,* 5324. (b) Li, X.; He, Li.; Chen, H.; Wu, W.; Jiang, H. *J. Org. Chem*. **2013**, *78*, 3636. (c) Tang, X.; Huang, L.; Yang, J.; Xu, Y.; Wu, W.; Jiang, H. *Chem. Commun.*, **2014**, *50*, 14793.

16. Fustero, S.; Rosell, M. S.; Barrio, P.; Sim, A. *Chem. Rev*. **2011**, *111*, 6984.

17. (a) Mano, N.; Kim, H. H.; Zhang, Y.; Heller, A. *J. Am. Chem. Soc.* **2002**, *124*, 6480. (b) Aggarwal, V. K.; Vicente, J. De.; Bonnert, R. V. *J. Org. Chem*. **2003**, *68*, 5381. (c) Taillefer, M.; Ouali, A.; Renard, B.; Spindler, J. F. *Chem. Eur. J*. **2006**, *12*, 5301. (d) Kaddouri, H.; Vicente, V.; Ouali, A.; Ouazzani, F.; Taillefer, M. *Angew. Chem. Int. Ed*. **2009**, *48*, 333.

18. (a) Rodriguez, A.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488. (b) Koradin, C.; Dohle, W.; Rodriguez, A.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571.

19. Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc*. **2001**, *123*, 2923

20. (a) Heutling, A.; Doye, S. *J. Org. Chem*. **2002**, *67*, 1961. (b) Bytschkov, I.; Doye, S. Eur. *J. Org. Chem*. **2003**, 935.

21. Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal*. **2002,** *344*, 795.

22. Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc*. **2004**, *126*, 1622.

23. Imahori, T.; Hori, C.; Knodo, Y. *Adv. Synth. Catal*. **2004**, *346*, 1090.

24. (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 439. (b) Ackermann, L.; Song, W.; Sandmann, R. *J. Organomet. Chem*. **2011**, *696*, 195.

25. (a) Sun, J.; Kozmin, S. A. *Angew. Chem., Int. Ed*. **2006**, *45*, 4991. (b) Y. Zhang, J. P. Donahue, Li, C. *J. Org. Lett*. **2007**, *9*, 627. (c) Alsabeh, P.G.; R. Lundgren, J.; Longobardi, L. E.; Stradiotto, M. *Chem. Commun*. **2011**, *47*, 6936.

26. (a) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun*. **2005**, 973. (b) Kantam, M. L.; Venkanna, G. T.; Kumar, K. B. S.; Subrahmanyam, V. B. *Chimica Acta* . **2010,** *93*, 974.

27. Tsuchimoto, T.; Aoki, K.; Wagatsuma,T.; Suzuki, Y. *Eur. J. Org. Chem.* **2008**, 4035.

28. (a) Das, U. K.; Bhattacharjee, M. *J. Organomet. Chem*. **2012**, *700*, 78. (b) Das, U. K.; Mandal, S.; Anoop, A.; Bhattacharjee, M. *J. Org. Chem*. **2014**, *79*, 9979.

29. Dvorko, M. Y.; Schmidt, E. Y.; Glotova, T. E.; Shabalin, D. A.; Ushakov, I. A.; Kobychev, V. B.; Petrushenko, K. B.; Mikhaleva, A. I.; Trofimov, B. A. *Tetrahedron* **2012**, *68*, 1963.

30. (a) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem. Int. Ed*, **2009**, *48*, 1138. (b) Verma, A. K.; Joshi, M.; Singh, V. P. *Org. Lett*. **2011**, *13*, 1630. (c) Joshi, M.; Patel, M.; Tiwari, R. K.; Verma, A. K. *J. Org. Chem*. **2012**, *77*, 5633. (d) Verma, A. K.; Jha, R. R.; Chaudhary, R.; Tiwari, R. K.; Reddy, K. S. K.; Danodia, A. *J.*

Org. Chem. **2012**, *77*, 8191. (e) Joshi, M.; Tiwari, R.; Verma, A. K. *Org. Lett*. **2012**, *14*, 1106. (f) Verma, A. K.; Patel, M.; Joshi, M.; Likhar, P. R.; Tiwari, R. K.; Parang, K. *J. Org. Chem*. **2014**, *79*, 172. (g) Patel, M.; Saunthawal, R. K.; Verma, A. K. *Tetrahedron Lett*. **2014**, *55*, 1310. (h) Patel, M.; Saunthawal, R. K.; Verma, A. K. *Acc. Chem*. *Res*. **2017**, *50*, 240.

31. (a) Patel, M.; Saunthawal, R. K.; Dhaked, D. K.; Bharatam, P. V.; Verma, A. K. *Asian J. Org. Chem*., **2015**, *4*, 894. (b) Patel, M.; Saunthawal, R. K.; Dhaked, D. K.; Bharatam, P. V.; Verma, A. K. *Asian J. Org. Chem*., **2016**, *5*, 213.

32. (a) Nimesh, H.; Sur, S.; Sinha, D.; Yadav, P.; Anand, P.; Bajaj, P.; Virdi, J. S.; Tandon, V. *J. Med. Chem.* **2014**, *57*, 5238. (b) Liang, Y.; Xie,Y. X.; Li, J. H. *J. Org. Chem.* **2006**, *71*, 379.