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Article

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Metal-free Cross-Dehydrogenative Coupling of *HN*-azoles with *α*-C(sp^3)-H amides *via* C-H activation and its Mechanistic and Application studies

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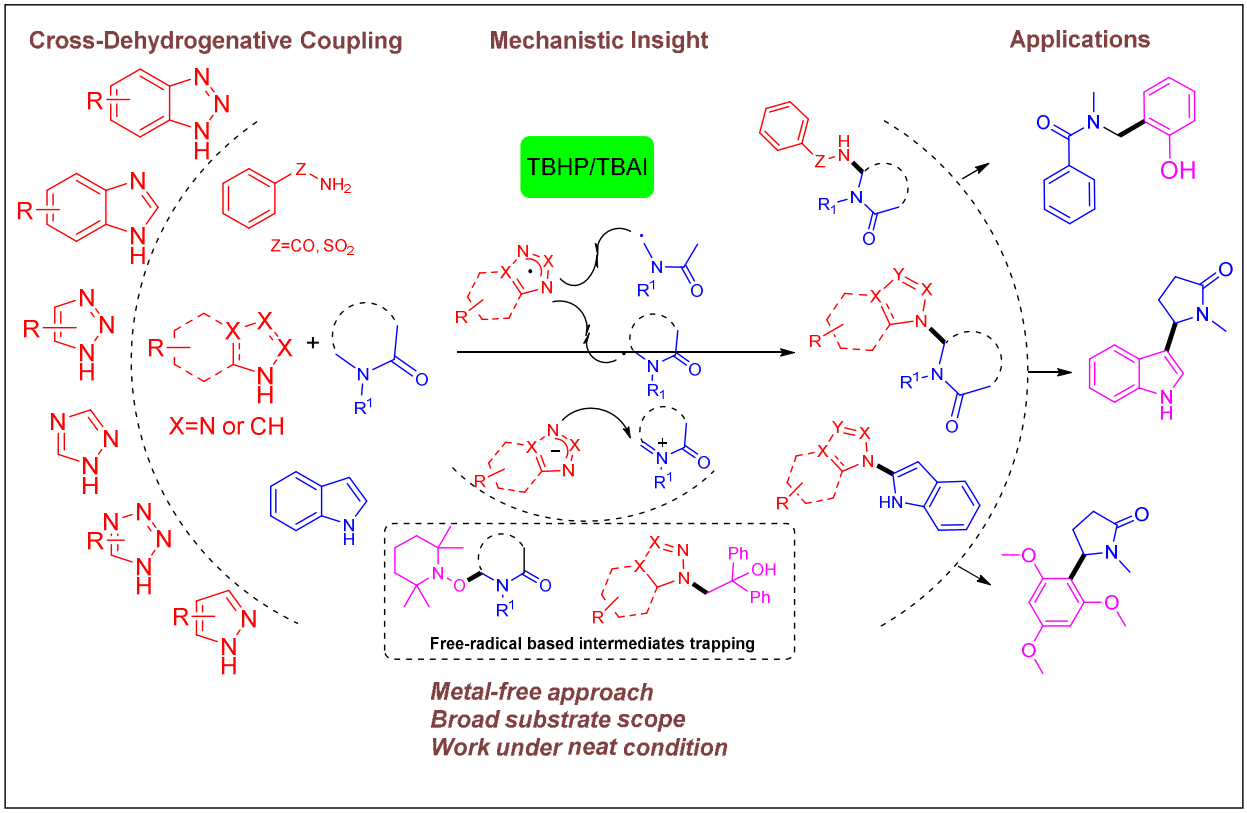


Abstract

A metal-free one step coupling reaction between various *N*-azole rings and diverse *α*-C(sp^3)-H containing amides have been developed under oxidative reaction conditions. Commercially available tetrabutyl ammonium iodide (TBAI) in the presence of terbutylhydroperoxide (TBHP), under neat reaction condition, efficiently catalysed the coupling. Various azole types such as 1*H*-benzotriazoles, 1*H*-1,2,3-triazoles, 1*H*-1,2,4-triazoles, 1*H*-tetrazoles, 1*H*-pyrazoles and 1*H*-benzimidazoles and *α*-C(sp^3)-H containing amides such as *N*,*N*-dimethylacetamide, *N*,*N*-dimethylbenzamide, *N*-methylacetamide, *N*-methylbenzamide, *N*-methylpyrrolidine and pyrrolidine-2-one were successfully employed for the coupling. A series of designed and controlled experiments were also performed in order to study the involvement of the different intermediates. Based on the evidences, a plausible mechanism is also proposed. These novel, simple, rapid, attractive and straightforward transformation open the way of the construction of novel highly functionalized *N*-azoles *via* direct covalent N-H bond transformations onto N-C bonds. This approach allows to the synthesis of complex molecules requiring number of steps using classical synthetic ways. In addition, the range of *α*-C(sp^3)-H

containing amide substrates is virtually unlimited highlighting the potential value of this simple system for the construction of complex heterocyclic molecules such as fused azoles derivatives.

Introduction:

C-H activation/functionalization methods provide unique and atom economy strategy for the functionalization and derivatization of sp^3, sp^2 and sp hybridized bonds.[1,2] In the last two decades, several transition-metals and metal-free catalytic systems were developed and successfully employed for such transformation. Among various catalytic systems, TBAI/TBHP has received significant attention because of its ease availability, economical and versatile redox potential. This catalytic system has been successful used in the construction of C-C, C-N, C-O and C-S bonds.[3-6] Recently, we have used TBAI/TBHP catalytic system for the activation of α-C(sp^3)-H bond of ethers/thioethers and successfully used for the coupling with azoles.[7] More importantly, activation of α-C(sp^3)-H bond of amides/amines will be of very high significance because of their ubiquitous occurrence and their presence in quite all biological systems. Amide derivatives were associated with broad spectrum of biological activities including, for instance, anticonvulsant, antituberculosis, antifungal, anticancer, analgesic-anti-inflammatory etc, generally coupled with diverse heterocycles.[8] According to our knowledge, only one approach is available for the construction of α-*N*-azolylamides, but involved iron catalytic system (Fig. 1).[9] As amides are ubiquitously present in both natural and synthetic chemical space for diverse biological and non-biological applications.[8] Consequently, facile and general methods for their functionalization are highly required, in order to extend the panel and the diversity of functionalized amides. While making this manuscript, Lakshman and co-workers also reported a Ru-catalyzed method for the coupling of *HN*-azoles with α-C(sp^3)-H bond containing ethers and also with amides but limited.[10] Here, we report metal-free TBAI/TBHP catalyzed method for the coupling of α-C(sp^3)-H of amides with azoles *via* α-C(sp^3)-H activation with wide and diverse substrate scope.

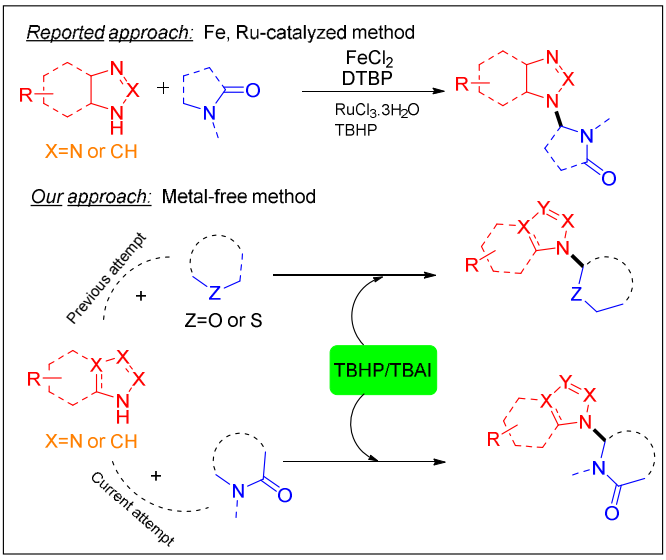


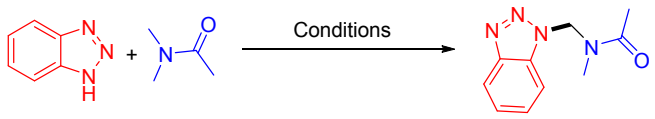
Figure 1. Approaches for functionalization of α-C(sp^3)-H amides

Results and Discussion:

1*H*-Benzotriazole (**1a**, Bt) and *N*,*N*-dimethylacetamide (**2a**, DMA) were firstly selected as a model substrate due to their simple chemical structure. In the first attempt, coupling reaction was performed in the presence of 2 equivalents of 70% aq. TBHP and 0.1 equivalent of TBAI in dichloroethane (DCE) as solvent (Table 1, entry a). N^1-coupled product **3a** was obtained in an isolated yield of 48%. In our next attempt, the amount of TBHP was increased to 3 equivalents, slight improvement in the yield of N^1-coupled product **3a** (52%) was observed (Table 1, entry b). Different solvents such as ethyl acetate (EtOAc), acetonitrile (ACN) didn't give any improvement (Table 1, entries c-d). Interestingly, when the reaction was performed under neat condition using DMA **2a** as a solvent, 68% of coupled product **3a** was observed (Table 1, entry e). In the further refinement, the reduction in the amount of DMA to 4 equivalents gave better result, wherein coupled product **3a** was observed in a yield of 72% (Table 1, entry f). Moreover, the reaction with non-aqueous TBHP (5-6 M in decane) have shown further improvement and coupled product **3a** was observed in a yield of 81% (Table 1, entry g). Further, reduction in the amount of DMA **2a** from 4 equivalents to 2 equivalents shown negative effect and only 36% of coupled product **3a** was noticed (Table 1, entry h). Other oxidants like DTBP and H_2O_2 did not give satisfactory results (Table 1, entry i-j). When the reaction was performed in the absence of TBAI, only 20% of product **3a** was observed (Table 1, entry k). Next, replacement of TBAI with

I_2, KI and NaI also catalysed the reactions and coupled product **3a** was observed in a yield of 76, 75 and 72% respectively (Table 1, entry l-n).

Table 1. Optimization studies[a]



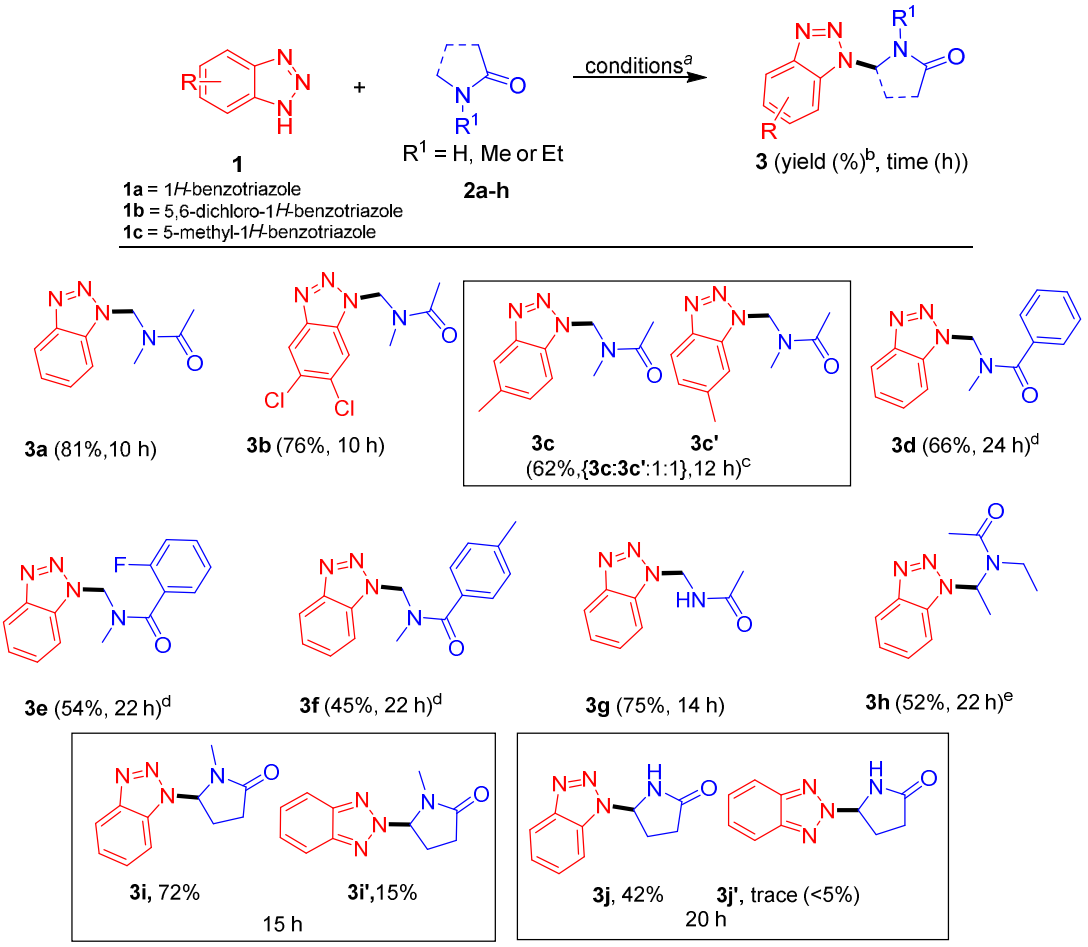
Entry	Oxidant (mmol)	Catalyst (0.025 mmol)	DMA (mmol)	Solvent	T (^oC)	Yield (%)[b]
a	Aq. TBHP (0.5)	TBAI	2.5	DCE	90	48
b	Aq. TBHP (0.75)	TBAI	2.5	DCE	90	52
c	Aq. TBHP (0.75)	TBAI	2.5	EtOAc	90	42
d	Aq. TBHP (0.75)	TBAI	2.5	ACN	90	Trace
e	Aq. TBHP (0.75)	TBAI	solvent	neat	100	68
f	Aq. TBHP (0.75)	TBAI	1	neat	110	72
g*	TBHP (0.75)	TBAI	1	neat	110	81
h*	TBHP (0.75)	TBAI	0.5	neat	110	36
i	DTBP (0.75)	TBAI	1	neat	110	24
j	H_2O_2 (0.75)	TBAI	1	neat	110	Trace
k*	TBHP (0.75)	-	1	neat	110	20
l*	TBHP (0.75)	I_2	1	neat	110	76
m*	TBHP (0.75)	KI	1	neat	110	75
n*	TBHP (0.75)	NaI	1	neat	110	72

[a]All the reactions were performed with 0.25 mmol of azole **1**. *TBHP (5-6 M in decane), 12 h. [b]Isolated yields.

Substituted 1*H*-benzotriazole such as 5,6-dichlorobenzotriazole reacted with DMA and produced N^1 coupling product **3b** in the yield of 76%. 5-Methylbenzotriazole underwent coupling with DMA **2a** and gave unseperable N^1 coupled regioisomers **3c** and **3c'** in an overall yield of 62%. Besides *N,N*-dimethylacetamide (DMA **2a**), 1*H*-benzotriazole **1a** also reacted smoothly with *N,N*-dimethylbenzamide **2b**, *o*-fluoro-*N,N*-dimethylbenzamide **2c** and *p*-methyl-*N,N*-dimethylbenzamide **2d**, afforded the corresponding N^1-selective coupled products **3d**, **3e**, and **3f** in an isolated yield of 66, 54, and 45 respectively. Subsequently, secondary aliphatic amide such as *N*-methylacetamide **2e** also reacted with 1*H*-benzotriazole **1a** and furnished 75% of N^1-selective coupled product **3g**. 1*H*-Benzotriazole **1a** also reacted with *N,N*-diethylacetamide **2f** gave **3h** in a yield of 52%. 1*H*-Benzotriazole **1a** on coupling with cyclic amide such as *N*-methylpyrrolidine **2g** (NMP) and gave separable mixture of N^1 and N^2 regio-isomers **3i** and **3i'**

with an isolated yield of 72 and 15%, respectively. On the other hand, 1*H*-benzotriazole **1a** also reacted with 2-pyrrolidinone **2h** and gave corresponding N^1-selective coupled product **3j** in a yield of 42% along with trace amount of N^2-selective other regio-isomer **3j'** (<5%) (Table 2).

Table 2. Coupling of un/substituted 1*H*-benzotriazoles with α-C(sp^3)-H containing amides

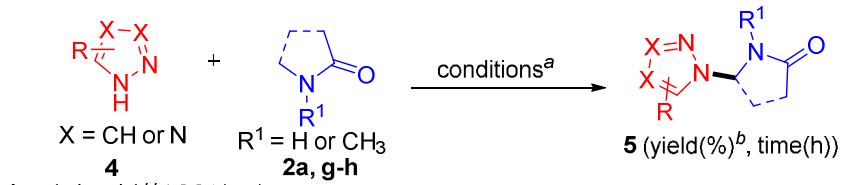


[a]Reaction conditions (unless otherwise noted): 1*H*-benzotriazole **1** (0.25 mmol), amides **2** (1 mmol), TBHP (0.75 mmol, 5-6 M in decane), TBAI (0.025 mmol) at 110 °C, [b]isolated yields, [c]Ratio was revealed by ^{1}H NMR and ^{13}C NMR. [d]Amide **2** (3 mmol) was used. [e]Reaction was performed in chlorobenzene solvent.

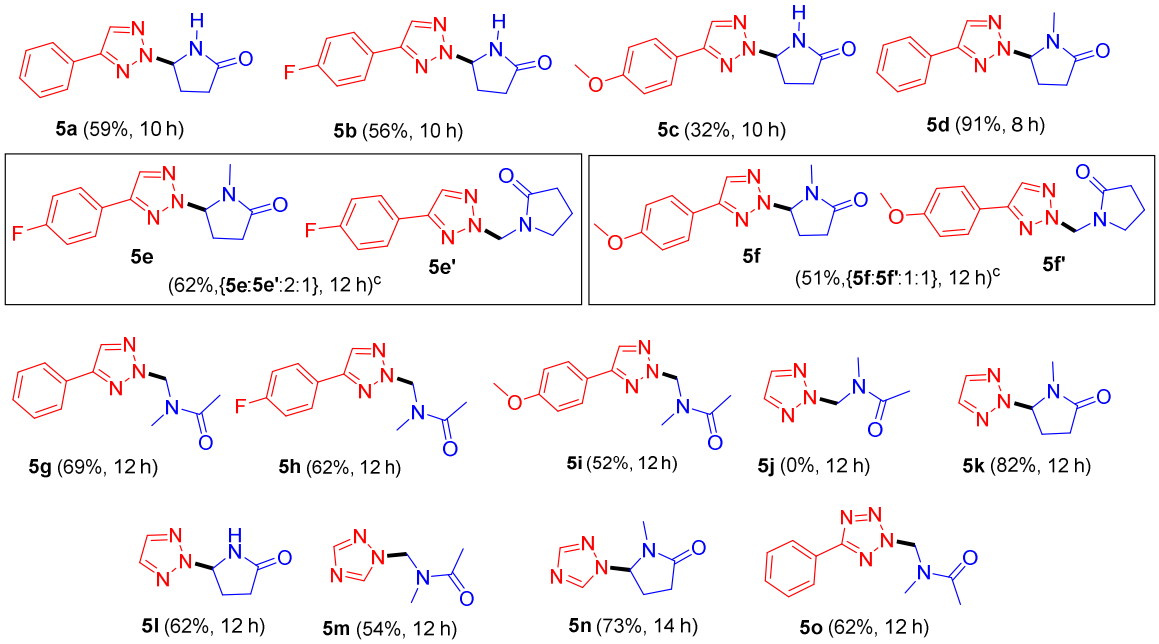
To further explore the diversity of optimized method, un/substituted 1*H*-1,2,3-triazoles, 1*H*-1,2,4-triazoles and 1*H*-tetrazoles **4** were also explored with α-C(sp^3)-H containing amides **2** and all the results are summarized in Table 3. 4-Phenyl-1*H*-1,2,3-triazole **4a** treated with pyrrolidine-2-one **2h** gave regioselective N^2 selective coupled product **5a**. The structure of **5a** is

unambiguously confirmed by X-ray analysis (details given on page No. 2 and 3 of SI). Similarly, 4-(4-fluorophenyl)-1*H*-1,2,3-triazole and 4-(4-methoxyphenyl)-1*H*-1,2,3-triazole on coupling with pyrrolidin-2-one **2h** also gave corresponding N^2-selective single regio-isomers **5b** and **5c** in an isolated yield of 56 and 32%, respectively. 4-Phenyl-1*H*-1,2,3-triazole **4a** also reacted efficiently with NMP **2g** and gave 91% of coupled product **5d**. The N^2-selectivity in **5d** was confirmed by HMBC and HSQC studies (details given on page No. 27 and 28 of supporting information). 5-(4-Fluorophenyl)-1*H*-1,2,3-triazole on coupling with NMP **2g** gave an un-separable mixture of regio-isomers **5e** and **5e'** in a ratio of 2:1 as predicted by NMR analysis. Similarly, 4-(4-methoxyphenyl)-1*H*-1,2,3-triazole also underwent coupling with NMP **2g** and gave an un-separable mixture of regio-isomers **5f** and **5f'** in a ratio of 1:1 with an overall yield of 51%. 4-Phenyl-1*H*-1,2,3-triazole **4a** when tried with DMA **2a**, 69% of N^2 regioselective product **5g** was observed, which was confirmed by HMBC and HSQC studies (details given on page No. 33 of supporting information). Similarly, 4-(4-fluorophenyl)-1*H*-1,2,3-triazole and 4-(4-methoxyphenyl)-1*H*-1,2,3-triazole also coupled with DMA **2a** and gave 62 and 51% of N^2-selective products **5h** and **5i**, respectively. Surprisingly, 1*H*-1,2,3-triazole **4b** did not give coupled product with DMA **2a**, but 1*H*-1,2,3-triazole when coupled with NMP **2g**, reaction underwent efficiently and gave the corresponding N^2-selective coupled product **5k** in an isolated yield of 82%. 1*H*-1,2,3-triazole also reacted with pyrrolidin-2-one **2h** and gave the corresponding N^2-selective products **5l** in an isolated yield of 62%. Interestingly, 1*H*-1,2,4-triazole **4c** underwent smooth coupling with both DMA **2a** and NMP **2g** and gave 54 and 73% of N^1 coupled products **5m** and **5n,** respectively. Under optimized conditions, 5-phenyl-1*H*-tetrazole **4d** also reacted with DMA **2a** and gave 62% of respective N^2-selective coupled product **5o**. Under optimised conditions, 5-phenyl-1*H*-tetrazole **4d** did not react with NMP **2g** and pyrrolidine-2-one **2h**.

Table 3. Coupling of un/substituted 1*H*-triazoles and 1*H*-tetrazole with α-C(sp^3)-H containing amides



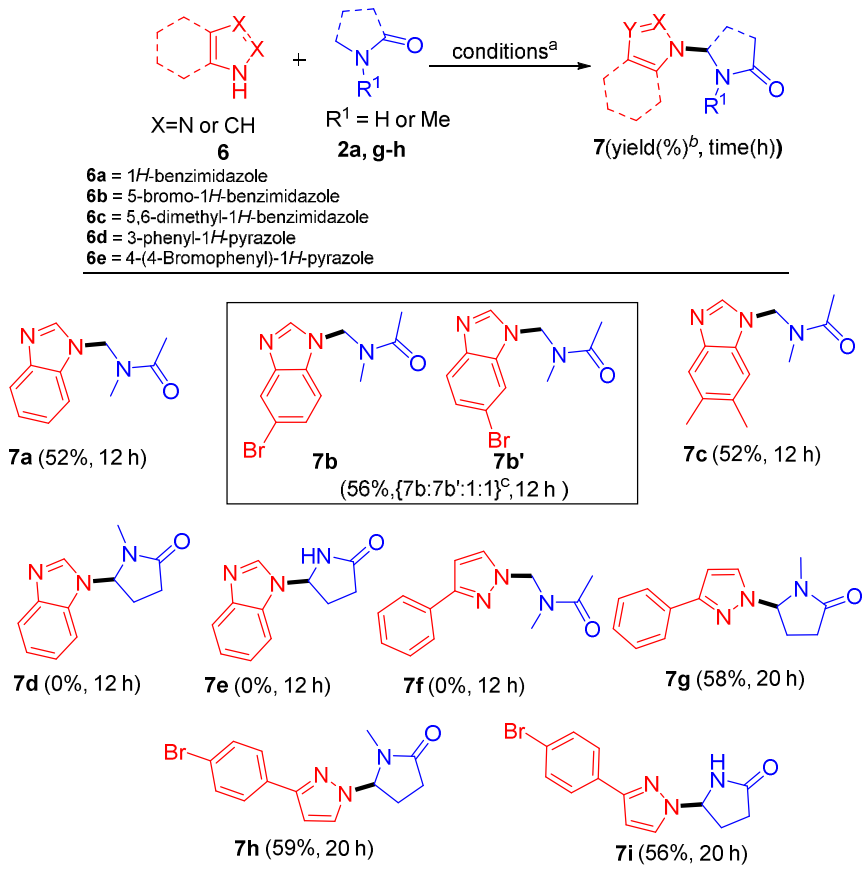
4a = 4-phenyl-1*H*-1,2,3-triazole
4b = 1*H*-1,2,3-triazole
4c = 1H-1,2,4-triazole
4d = 5-phenyl-1H-tetrazole



[a]Reaction conditions: azole **4** (0.25 mmol), amide **2** (1 mmol), TBHP (0.75 mmol, 5-6 M in decane), TBAI (0.025 mmol), 110 °C. [b]Isolated yields. [c]Ratio was revealed by ^{1}H NMR and ^{13}C NMR.

Next, other azoles such as un/substituted 1*H*-benzimidazoles and 1*H*-pyrazoles **6** were also tried under optimized conditions. To our delight, both the substrates underwent reaction with α-C(sp^3)-H containing amides **2** and gave respective coupled products in moderate to good yields (Table 4). 1*H*-Benzimidazole **6a** on reaction with DMA **2a** gave 52% of coupled product **7a**. 5-Bromo-1*H*-benzimidazole **6b** on reaction with DMA **2a**, gave mixture of un-separable N^1/N^2 regio-isomers **7b** and **7b'** with overall yield of 56%. Similarly, 5,6-dimethyl-1*H*-benzimidazole **6c** on reaction with DMA **2a** furnished **7c** in a yield of 52% respectively. 1*H*-benzimidazole did not work with NMP **2g** and pyrrolidin-2-one **2h**. Further, 3-phenyl-1*H*-pyrazole **6d** didn't couple with DMA **2a** but underwent smooth coupling with cyclic amide such as NMP **2g** and gave 58% of corresponding coupled product **7g**. 3-(4-Bromophenyl)-1*H*-pyrazole **6d** when tried with NMP **2g** and pyrrolidin-2-one **2h**, corresponding N^1 coupled products **7h** and **7i** were formed in a yield of 59 and 56%, respectively.

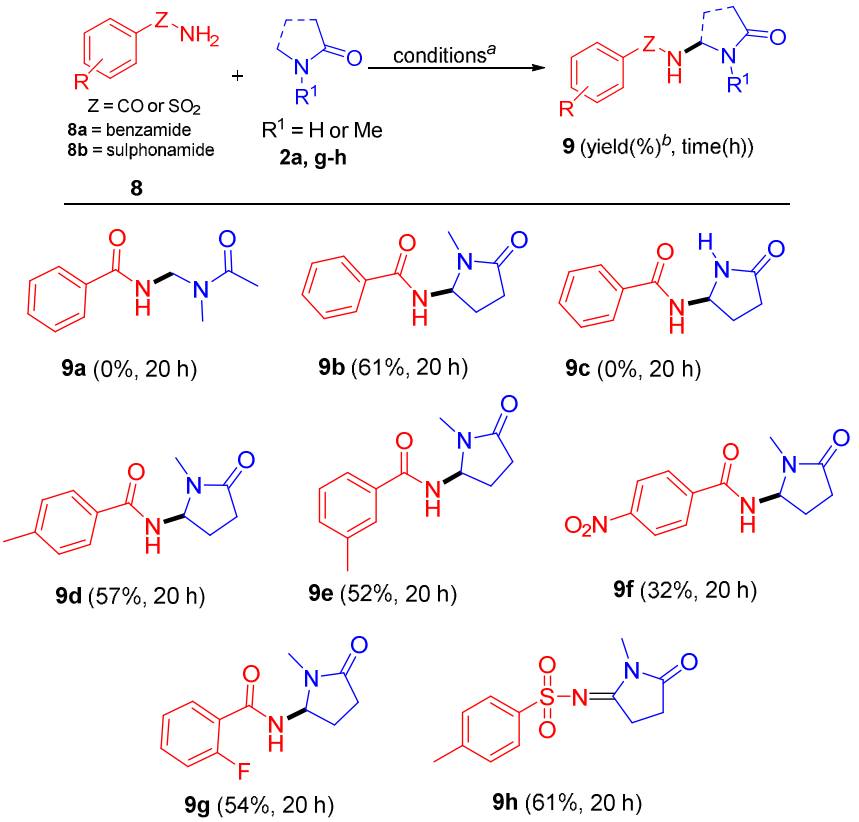
Table 4. Coupling of un/substituted 1*H*-benzimidazole or 1*H*-pyrazole with α-C(sp^3)-H containing amides



[a]Reaction conditions: azole **6** (0.25 mmol), amide **2** (1 mmol), TBHP 5-6 M in decane (0.75 mmol,), TBAI (0.025 mmol) 110 ^{o}C. [b]Isolated yields are shown. [c]ratio was revealed by ^{1}H NMR and ^{13}C NMR.

We next examined other nucleophiles **8** such as benzamides **8a** and sulphonamide **8b** with α-C(sp^3)-H containing amides **2** (Table 5). Under optimized conditions, benzamide **8a** didn't couple with DMA **2a**, however, underwent reaction with NMP **2g** and gave 61% of corresponding coupled product **9b**. Under optimized conditions, benzamide **8a** didn't couple with pyrrolidine-2-one **2h**. Other substituted benzamide containing both donating (*p*-methyl and *m*-methyl) and electron-withdrawing (*p*-nitro and *o*-fluoro) groups also underwent coupling with NMP **2g** and gave corresponding coupled products **9d**, **9e**, **9f** and **9g** in a yield of 57, 52, 32 and 54% respectively. 4-Methylbenzenesulfonamide **8b** when tried with NMP **2g**, gave a coupled product **9h** in a yield of 61%.

Table 5. Coupling of un/substituted benzamides with α-C(sp^3)-H containing amides



[a]Reaction conditions: benzamide or sulphonamide **8** (0.25 mmol), amide **2** (1 mmol),TBHP 5-6 M in decane (0.75 mmol), TBAI (0.025 mmol), 110 °C. [b]Isolated yields are shown.

The practicality of the present method was also seen by performing a gram scale synthesis of **3a** (0.92 g, 53%), suggesting that the method could also be efficiently scaled up (Fig. 2).

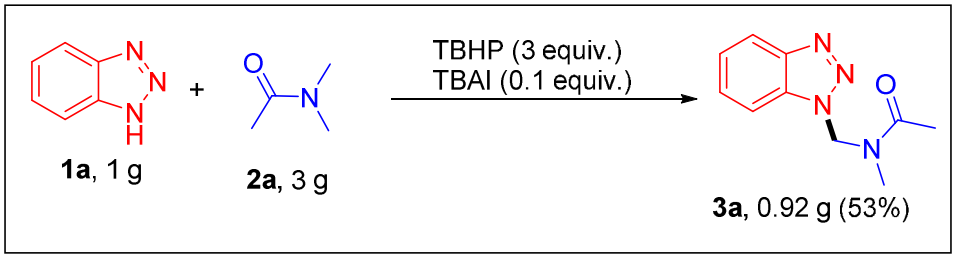


Figure 2. Gram scale synthesis of compound **3a**

Since 1985, after Katritizky's report, benzotriazolyl (Bt) moiety has been highly exploited as synthetic auxiliary and has been used in numerous synthetic transformations ranging from simple functionalization to the construction of heterocycles.[11]. In the present study, the synthesized *α*-benzotriazolyl containing amides have also been further explored for the synthesis of useful synthetic intermediates and heterocycles (Fig 3). For instances, *α*-benzotriazolyl containing DMA **3d** when reacted with phenol in the presence of Lewis acid gave *N*-(substituted)benzyl-*N*-methylbenzamide **10**. Likewise, *α*-benzotriazolyl containing NMP **3i** on reaction with 1*H*-indole and 1,3,5-trimethoxybenzene and gave 5-indolylpyrolidinone **11** and 5-aryl-*N*-methylpyrrolidinone **12** respectively with excellent yields.

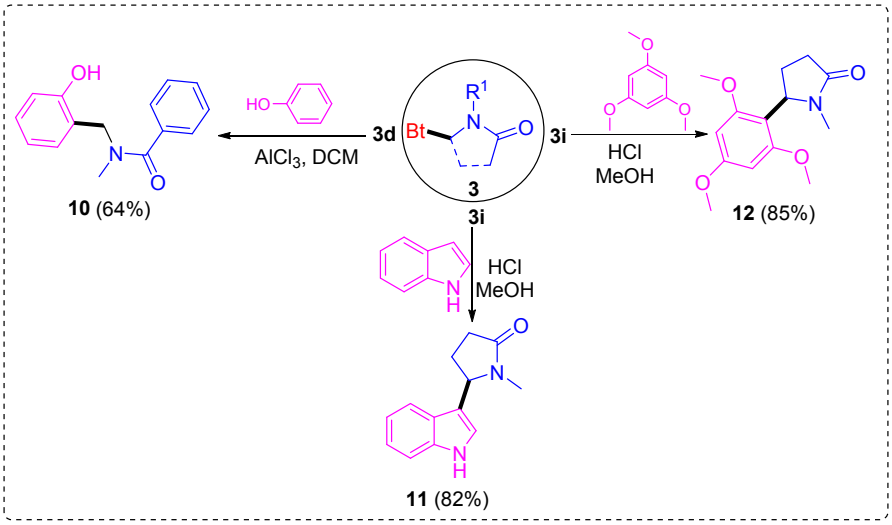
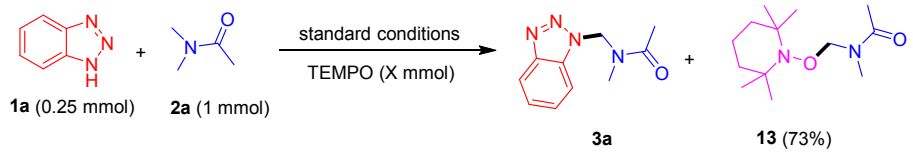


Figure 3. Synthetic elaboration of *α*-Bt containing amides

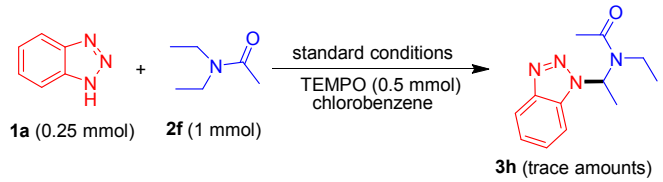
During diversity generation, the obtained results indicated that coupling partners participated through ionic and radical based intermediates and their existence is highly depends upon the structures of substrates. To ascertain the mechanism involved, and several control experiments were performed (all results are depicted in Fig. 4. In first instance, the nature of amide base intermediate were established by performing the experiment in the presence of free-radical scavenger *viz*., 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO). The reaction of Bt **1a** with DMA **2a** in the presence TEMPO was performed, the yield of coupled product **3a** was significantly suppressed and instead TEMPO-DMA adduct **13** was formed (eq. 1). Next, reaction of Bt **1a** with DEA **2f** in the presence free-radical scavenger *viz*., 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was performed, the yield of coupled product **3h** was also significantly suppressed (eq. 2). Surprisingly, when reaction of Bt **1a** with NMP **2g** in the presence 2 equivalent of

TEMPO was performed, 62% of TEMPO-NMP adduct **14** was obtained along with considerable amount of coupled product **3i**. The formation of coupled product **3i** was also noticed even when 5 equivalent of TEMPO was used (eq. 3). These results suggested that open chain amides participated through purely radical pathway and cyclic amides participated through radical and ionic path way. In case, the NMP **2g**, the formation of coupled products suggested the fast conversion of radical based intermediate into ionic *via* second electron transfer reaction. In another attempts, to confirm the nature of diverse azoles and nucelophiles, reactions in the presence of another free-radical scavenger, 1,1-diphenylethylene (DPE) were also performed (eq. 4 to 12). These results suggested that benzo-fused azoles and phenyl substitutedazoles participated through radical based intermediates, as confirmed by the formation of their adducts with DPE (**15**, **16**, **17**, **18** and **19**). The structure of compound **16** was also confirmed by X-ray analysis (details given on page No. 3 and 4 of SI). On the other hand, simple azoles and benzamides and sulphonamides attack as neutral nucleophiles. In order to rule out the involvement of iodine mediated coupling of azoles with DPE, an experiment was conducted between 1*H*-benzotriazole **1a** and DPE in the absence of TBAI (eq. 13). The reaction gave expected coupled product **15**, ruled out the possibility of iodine mediation.

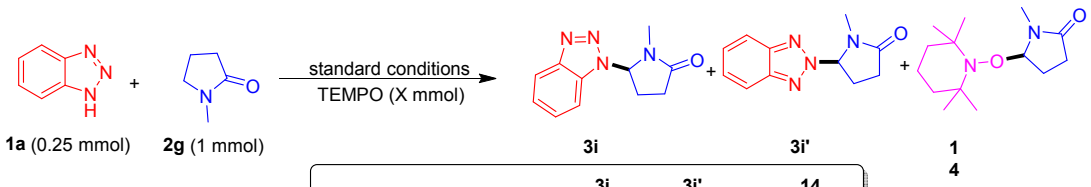


1a (0.25 mmol) + **2a** (1 mmol) → **3a** + **13** (73%) eq. 1

	3a	13
TEMPO (0.5 mmol)	~10%	73%
TEMPO (1.25 mmol)	<3%	95%

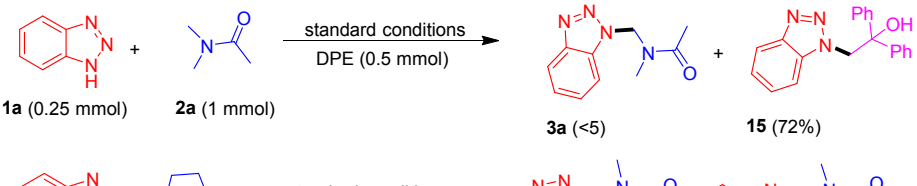


1a (0.25 mmol) + **2f** (1 mmol) → **3h** (trace amounts) eq. 2

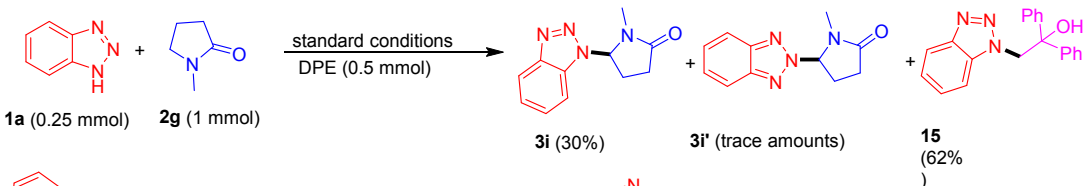


1a (0.25 mmol) + **2g** (1 mmol) → **3i** + **3i'** + **14** eq. 3

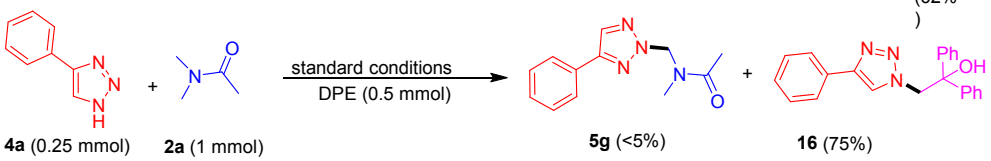
	3i	3i'	14
TEMPO (0.5 mmol)	~30%	trace	62%
TEMPO (1.25 mmol)	~25%	trace	80%



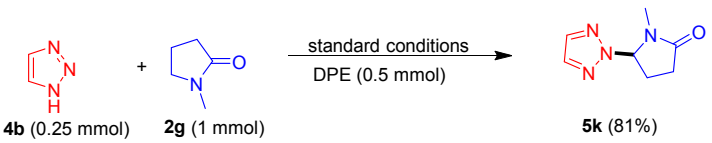
1a (0.25 mmol) + **2a** (1 mmol) → **3a** (<5) + **15** (72%) eq. 4



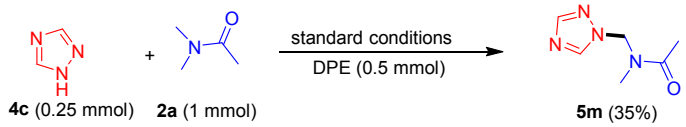
1a (0.25 mmol) + **2g** (1 mmol) → **3i** (30%) + **3i'** (trace amounts) + **15** (62%) eq. 5



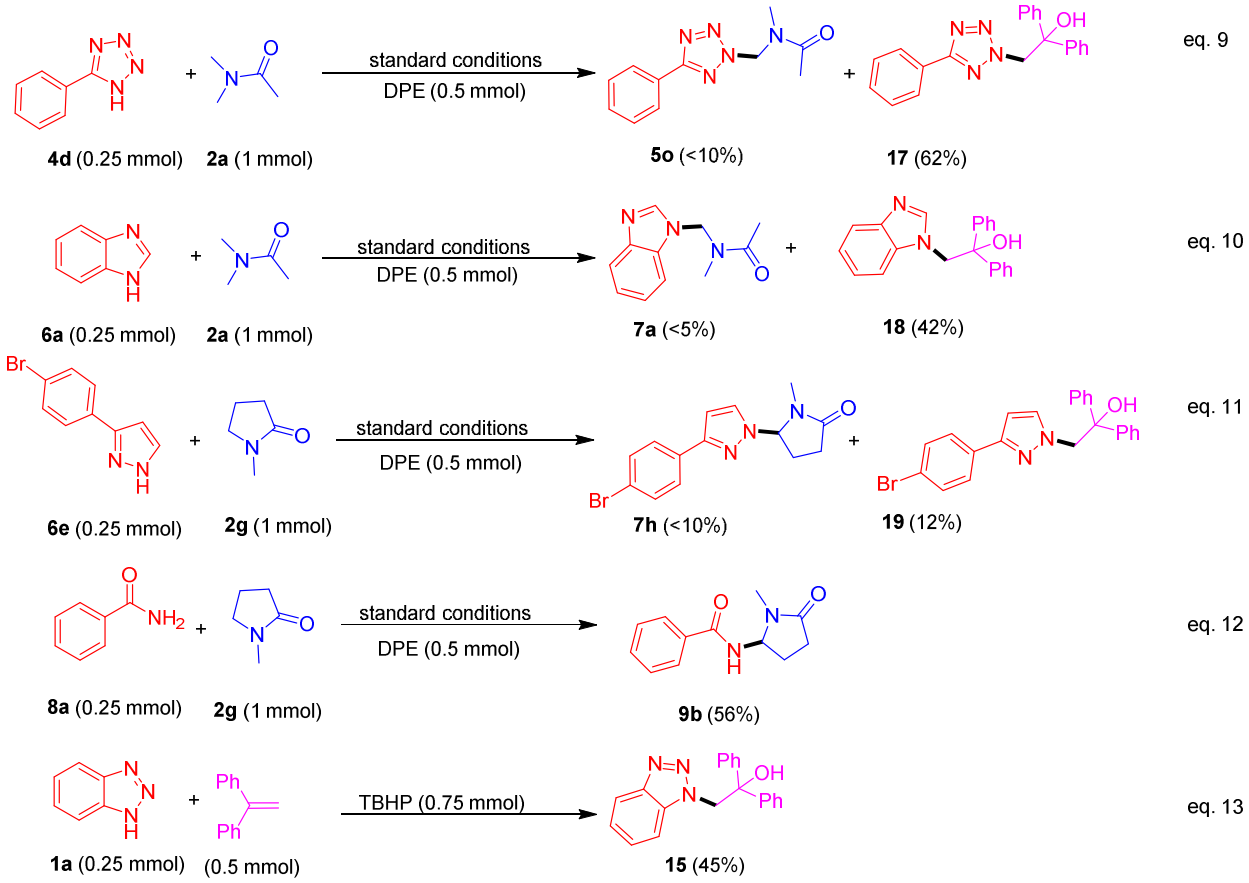
4a (0.25 mmol) + **2a** (1 mmol) → **5g** (<5%) + **16** (75%) eq. 6



4b (0.25 mmol) + **2g** (1 mmol) → **5k** (81%) eq. 7



4c (0.25 mmol) + **2a** (1 mmol) → **5m** (35%) eq. 8



[a]Standard conditions: azole (0.25 mmol), amide (1 mmol), TBHP (0.75 mmol, 5-6 M in decane), TBAI (0.025 mmol), 110 °C. [b]Isolated yields are shown.

Figure 4. Control experiments

Based on the above control experiments, we could postulates that the reactions proceeded through the involvement of radical and ionic based intermediates and fate is decided by the nature of azoles and α-C(sp^3)-H containing amides. Among the diverse azoles tried, it seems that benzo-fused azoles and phenyl substituted azoles such as 1*H*-benzotriazole **1a**, 4-phenyl-1*H*-1,2,3-triazole **4a**, 1*H*-1,2,4-triazole **4c**, 1*H*-tetrazole **4d** and 1*H*-benzimidazole/3-phenyl-1*H*-pyrazoles **6** proceeded through radical based inetrmediates. On the other hand, azoles such as 1*H*-1,2,3-triazole and other nucleophiles such as benzamide and sulfonamide **8** operated through only ionic pathway. Among α-C(sp^3)-H amides **2**, it seems that DMA **2a** operated through only radical based intermediate and therefore work with azoles capable of generating radical based intermediates such as 1*H*-benzotriazole **1a**, 4-phenyl-1*H*-triazole **4a**, 1*H*-benzimidazole **6a**, 1*H*-1,2,4-triazole **4c**, 5-phenyl-1*H*-tetrazole **4d**. On the other hand, NMP **2g** is operated through both radical and iminium based intermadiates and that could be the reason worked with all azoles and

nucleophiles such as benzamides and sulfonamides **8**. The non-coupling of 1*H*-benzimidazole **6a** and 5-phenyl-1*H*-tetrazole **4d** with NMP **2g** might be due to some steric factor. Furthermore, in case of cyclic amides, the convesrion of radical based intermediates might be very fast, and explain the reason why reaction with NMP **2g** in the presence of free-radical scavanger didn't get completely suppressed, while with DMA **2a**, the presence of free-radical scavanger almost completely supressed the formation of coupled products.

Based on the control experiments and the literature precedents, the following plausible pathways are being proposed as shown in the Fig 5. The present reaction is initiated by redox reaction between TBAI and TBHP, which generates *tert*-butoxy and *tert*-butylhydroperoxide radicals. Under present oxidative conditions, α-C(sp^3)-H amides generates the corresponding radical species **2a'** and **2'** (step-i) *via* interaction with either *tert*-butoxy or *tert*-butylhydroperoxide radicals (which in turn produced from TBAI and TBHP). The further fate of the radicals **2a** or **2a'** depends upon the nature of amides, open chain amides such as *N,N*-dimethylacetamide **2a**, *N,N*-dimethylbenzamide **2b** and *N*-methylacetamide **2c** didn't generate iminiun ion and reacted through radical-based intermediates **2a'** with azoles capable of generates radical. On the other hand, cyclic amides such as NMP **2g** and pyrrolidin-2-one **2h** underwent further electron transfer reaction (step ii) and generates iminiun ions **2''**, which then coupled with azoles as well as nucleophilic partners such as benzamides and sulfonamides to furnished coupled products.

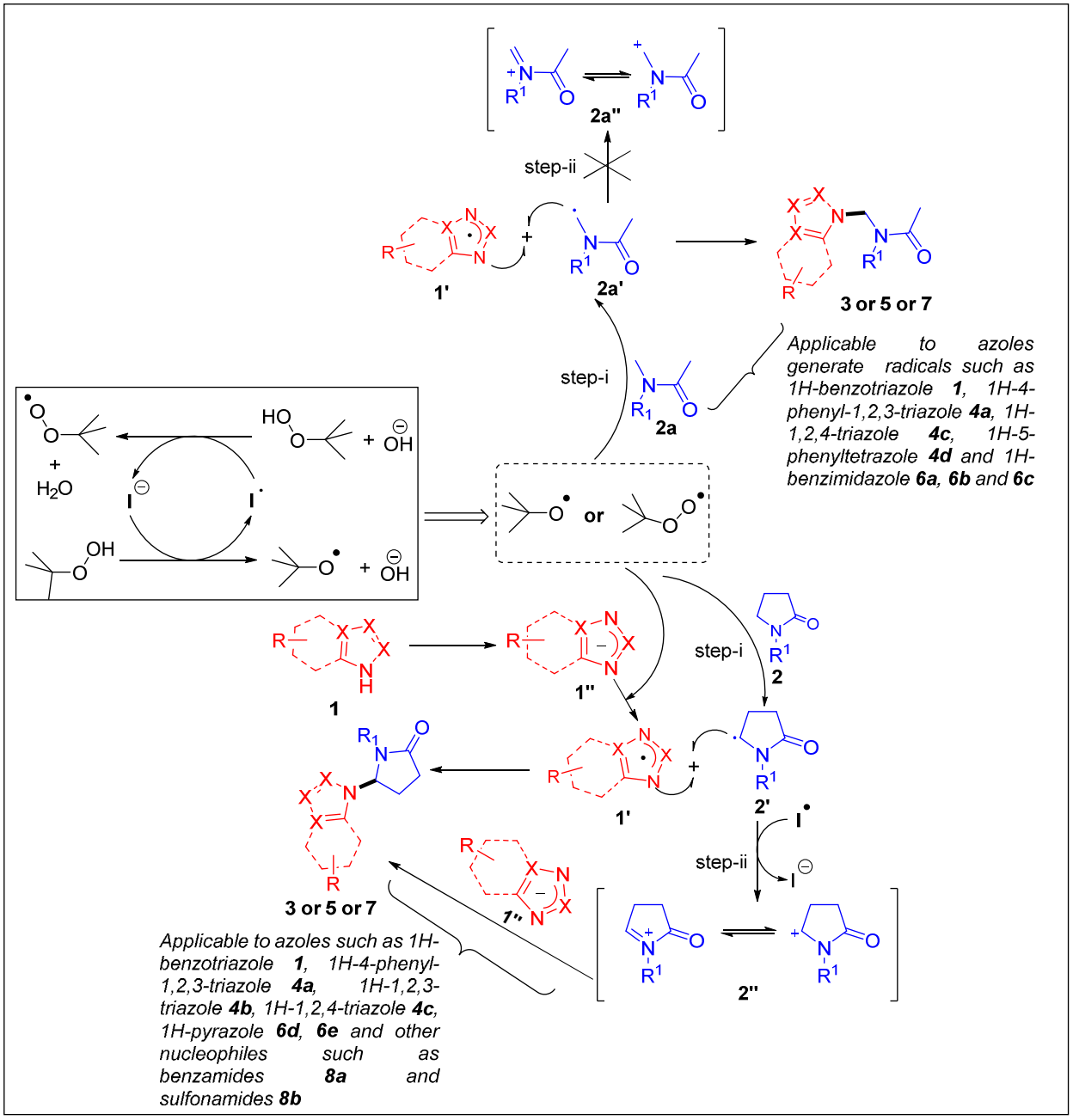
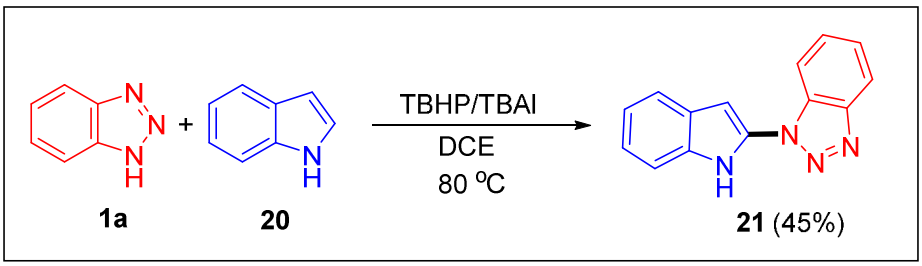


Figure 5. Plausible mechanism

As the present method generates azole-based radical, which convert the nucleophilic azoles into electron-deficient azoles, and also providing the chance of further exploitation. In this direction, a reaction has been planned for the coupling of azoles with electron-rich heteroarenes such as *NH*-indole. Under TBAI/TBHP conditions, when 1*H*-benzotriazole was treated with 1*H*-indole **20**, coupling underwent and C2-coupled product **21** was observed in a yield of 45% (Table 6).

Table 6. Coupling of 1*H*-indole with 1*H*-1,2,3-benzotriazole



In conclusion, a metal free, TBAI/TBHP mediated cross-dehydrogenative coupling between N*H*-azoles and α-C(sp^3)-H containing amides has been developed. Apart from azoles, nucleophiles such as benzamides and sulfonamides also underwent coupling with NMP under TBAI/TBHP conditions. The synthesized α-benzotriazolyl containing amides were further exploited for the C-C bond formation reactions and prepared DMA and NMP based synthetic compounds. The present study first time reported the existence of azole-based radicals, which umpolung the reactivity of azoles, and further demonstrated its coupling with electron-rich coupling partner 1*H*-indole.

Experimental section:

General Information:

Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F254 (20 x 20 cm). TLC plates were visualized by exposing UV light or by iodine vapours or immersion in an acidic staining solution of *p*-anisaldehyde followed by heating on a hot plate. Organic solvents were concentrated by rotary evaporation. Column chromatography was performed on flash silica gel of 100-200 mesh size using EtOAc and hexane or MeOH and DCM solvent system. Melting points were recorded on melting point instrument and were uncorrected. ^{1}H NMR spectra were recorded with 400 MHz NMR instrument. Chemical data for protons are reported in parts per million (ppm, scale) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.26 or other solvents as mentioned). Mass spectra were recorded with LCMS-QTOF instrument. The coupling constant (*J*) are mentioned in Hz. ESI-MS and HRMS spectra were recorded on LC-Q-TOF and HRMS-UHD machines.

Experimental section:

General procedure for the coupling of *HN*-azole (1, 4 and 6) and benzamide or sulphonamide (8) with *α*-C(sp^3)-H amides (2): (Table 2, 3, 4 and 5)

To a 50 ml sealed tube with magnetic bar, *HN*-azoles **(1, 4 and 6**) and benzamides or sulphonamides (**8**) (0.25 mmol) and *α*-C(sp^3)-H amides **2** (1 mmol) was loaded. *tert*-Butylhydroperoxide (5-6 M in Decane) 0.75 mmol was added followed by the addition of tetrabutylammonium iodide (0.025 mmol). Reaction mixture was allowed to stir at 110 ^{o}C. Progress of reaction was monitored by TLC. After completing reaction, required product **3**, **5**, **7** and **9** was obtained on column chromatography (100-200 mesh size) using EtOAc and hexane (6:4) as eluents. Compounds **5m**, **5n**, **5o**, **7a**, **7b**, **7c**, **9b**, **9d**, **9e**, **9f** and **9g** were purified column chromatography (100-200 mesh size) using MeOH and DCM (2:98) as eluents.

Note: In case of products **5g**, **5h**, **5i** and **5o**, rotamers have been noticed. The rotamers leads to duplication in spectra of **5g**, **5h**, **5i** and **5o**.

Spectral data:

***N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-*N*-methylacetamide [9] (3a, Table 2)**

TLC R_f=0.5 **(**40% EtOAc/Hexane**)**; Yield 81% (41 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.13 (s, 2H), 3.03 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 146.0, 132.3, 127.9, 124.4, 119.5, 111.0, 57.5, 34.9, 21.7; HRMS (ESI+) calcd. for: $C_{10}H_{12}N_4NaO$ 227.0909. (M+ Na), found 227.0904.

***N*-((5,6-dichloro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-*N*-methylacetamide (3b, Table 2)**

TLC R_f=0.5 **(**40% EtOAc/Hexane**)**; Yield 76% (51 mg); Grey color solid; m.p.: 152-154 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 8.01 (s, 1H), 6.03 (s, 2H), 3.04 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 144.9, 133.2, 131.5, 129.4, 120.4, 112.6, 58.0, 35.2, 21.7; HRMS (ESI+) calcd. for: $C_{10}H_{11}Cl_2N_4O$ 273.0310. (M+ H), found 273.0297.

***N*-methyl-*N*-((5-methyl-1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)acetamide and *N*-methyl-*N*-((6-methyl-1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)acetamide (3c, Table 2)**

TLC R_f=0.5 **(**40% EtOAc/Hexane**)**; Yield 62% (33.8 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.81 – 7.66 (m, 2H), 7.60 (s, 1H), 7.29 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.18 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.14 (d, *J* = 5.3 Hz, 4H), 3.07 (d, *J* = 6.5 Hz, 5H), 2.49 (d, *J* = 8.0 Hz, 6H), 2.10 (d, *J* = 5.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 171.6, 146.7,

144.7, 138.7, 134.5, 132.8, 130.8, 130.1, 126.7, 119.0, 118.4, 110.5, 110.0, 57.5, 57.3, 34.9, 29.7, 22.0, 21.7, 21.5; HRMS (ESI+) calcd. for: $C_{11}H_{15}N_4O$ 219.1246. (M+ H), found 219.1249.

***N*-((1*H*-benzo[*d*][1,2,3]triazol-1yl)methyl)-*N*-methylbenzamide [12] (3d, Table 2)**

TLC R_f=0.6 **(**40% EtOAc/Hexane**)**; Yield 66% (43 mg); Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 2H), 7.65 – 7.37 (m, 7H), 6.46 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 146.2, 134.6, 132.4, 130.5, 128.5, 128.1, 127.0, 124.5, 119.7, 111.0, 58.0, 36.4; HRMS (ESI+) calcd. for: $C_{15}H_{15}N_4O$ 267.1246. (M+ H), found 267.1240.

***N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-2-fluoro-*N*-methylbenzamide (3e, Table 2)**

TLC R_f=0.6 **(**40% EtOAc/Hexane**)**; Yield 54% (38 mg); White solid; m.p.: 127-128 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.42 (dd, *J* = 13.7, 6.5 Hz, 2H), 7.35 (t, *J* = 7.1 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 9.0 Hz, 1H), 6.42 (s, 2H), 2.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 158.1 (d, $J_{(C-F)}$ = 247.5 Hz), 146.2, 132.3, 132.1 (d, $J_{(C-F)}$ = 7.4 Hz), 132.0, 128.9 (d, $J_{(C-F)}$ = 3.7 Hz), 128.1, 124.5, 119.7, 115.9 (d, $J_{(C-F)}$ = 21 Hz), 111.0, 57.5, 35.0; HRMS (ESI+) calcd. for: $C_{15}H_{14}FN_4O$ 285.1152. (M+ H), found 285.1159.

***N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-*N*,4-dimethylbenzamide (3f, Table 2)**

TLC R_f=0.6 **(**40% EtOAc/Hexane**)**; Yield 45% (45 mg); White solid; m.p.:142-143 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.50 – 6.99 (m, 7H), 6.31 (s, 2H), 2.98 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 146.2, 140.9, 132.5, 131.6, 129.1, 128.0, 127.3, 124.4, 119.7, 111.0, 58.2, 36.3, 21.4; HRMS (ESI+) calcd. for: $C_{16}H_{17}N_4O$ 281.1402. (M+ H), found 281.1406.

***N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)acetamide (3g, Table 2)**

TLC R_f=0.6 **(**60% EtOAc/Hexane**)**; Yield 75% (35 mg); White solid; m.p.: 130-132 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4, Hz, 1H), 7.51 (t, *J* = 9.4 Hz, 1H), 7.42 – 7.35 (t, 9.2 Hz, 1H), 7.23 (broad singlet, 1H), 6.10 (d, *J* = 6.9 Hz, 2H), 2.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 145.9, 132.4, 128.0, 124.4, 119.4, 111.0, 50.8, 23.1; HRMS (ESI+) calcd. for: $C_9H_{10}N_4NaO$ 213.0752. (M+Na), found 213.0759.

***N*-(1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)ethyl)-*N*-ethylacetamide (3h, Table 2)**

TLC R_f=0.5 (40% EtOAc/Hexane); Yield 52% (30 mg); Colorless liquid; ^{1}H NMR (400 MHz, CDCl3) δ 8.05 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.62 (q, *J* = 6.9 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.41 – 7.36 (m, 1H), 3.43 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.32 (dq, *J* = 14.4, 7.2 Hz, 1H),

2.15 (s, 3H), 2.10 (d, *J* = 7.0 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 145.8, 132.6, 127.7, 124.4, 119.6, 110.6, 60.8, 37.5, 21.5, 17.7, 15.5; HRMS (ESI+) calcd. for: $C_{12}H_{17}N_4O$ 233.1402. (M+ H), found 233.1409.

5-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-1-methylpyrrolidin-2-one [10] (3i, Table 2)

TLC R_f=0.3 **(**70% EtOAc/Hexane**)**; Yield 72% (39 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 1H), 7.59 – 7.50 (m, 1H), 7.49 – 7.40 (m, 2H), 6.51 (dd, *J* = 8.5, 2.7 Hz, 1H), 2.91 (ddt, *J* = 13.0, 9.0, 4.8 Hz, 2H), 2.74 – 2.63 (m, 4H), 2.54 – 2.43 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 146.6, 131.2, 128.4, 124.6, 120.7, 108.9, 74.6, 29.3, 27.6, 25.0; HRMS (ESI+) calcd. for: $C_{11}H_{13}N_4O$ 217.1089. (M+ H), found 217.1095.

5-(2*H*-benzo[*d*][1,2,3]triazol-2-yl)-1-methylpyrrolidin-2-one [10] (3i', Table 2)

TLC R_f=0.6 **(**70% EtOAc/Hexane); Yield 15% (8 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.35 (dd, *J* = 6.6, 3.1 Hz, 2H), 6.23 (dd, *J* = 7.6, 1.3 Hz, 1H), 2.96 (dt, *J* = 12.1, 6.9 Hz, 1H), 2.71 – 2.55 (m, 4H), 2.55 – 2.40 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 144.5, 127.0, 118.4, 80.6, 28.8, 27.8, 25.8; HRMS (ESI+) calcd. for: $C_{11}H_{13}N_4O$ 217.1089. (M+ H), found 217.1093.

5-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)pyrrolidin-2-one (3j, Table 2)

TLC R_f=0.3 (70% EtOAc/Hexane); Yield 42% (21 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.30 (dd, *J* = 8.1, 7.1 Hz, 1H), 6.44 (d, *J* = 6.1 Hz, 1H), 2.77 (dq, *J* = 13.4, 8.1 Hz, 2H), 2.66 – 2.53 (m, 1H), 2.50 – 2.34 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 146.3, 131.4, 128.0, 124.4, 120.2, 109.4, 68.6, 29.0, 27.6; HRMS (ESI+) calcd. for: $C_{10}H_{11}N_4O$ 203.0933. (M+ H), found 203.0939.

5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrrolidin-2-one (5a, Table 3)

TLC R_f=0.2 **(**60% EtOAc/Hexane**)**; Yield 59% (33 mg); White solid; m.p.: 124-125 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.76 (d, *J* = 7.3 Hz, 2H), 7.4 (m, 2H), 7.36 (m, 1H), 7.01 (broad, 1H), 6.19 (d, *J* = 6.7 Hz, 1H), 3.01 – 2.81 (m, 1H), 2.68 (dd, *J* = 16.2, 8.9 Hz, 2H), 2.43 (ddd, *J* = 16.9, 8.9, 2.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 146.7, 129.9, 128.0, 127.0, 126.9, 124.0, 71.2, 26.5, 25.7; HRMS (ESI+) calcd. for: $C_{12}H_{13}N_4O$ 229.1089. (M+ H), found 229.1085.

5-(4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)pyrrolidin-2-one (5b, Table 3)

TLC R_f=0.2 **(**60% EtOAc/Hexane**)**; Yield 56% (34 mg); White solid; m.p.: 131-133 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.73 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 7.14 (broad, 1H), 6.17 (d, *J* = 6.8 Hz, 1H), 2.95 – 2.82 (m, 1H), 2.77 – 2.60 (m, 2H), 2.42 (ddd, *J* = 16.8, 8.9, 2.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 163.0 (d, $J_{(C-F)}$ = 246.2 Hz), 147.7, 131.5, 127.7 (d, $J_{(C-F)}$ = 8.7 Hz), 126.1 (d, $J_{(C-F)}$ = 3.7 Hz), 116.0, 73.2, 28.4, 27.5; HRMS (ESI+) calcd. for: $C_{12}H_{11}FN_4NaO$ 269.0815 (M+ H), found 269.0806.

5-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)pyrrolidin-2-one (5c, Table 3)

TLC R_f=0.2 **(**60% EtOAc/Hexane**)**; Yield 32% (21 mg); White solid; m.p.: 141-142 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.66 (s, 1H), 6.16 (dd, *J* = 5.3, 2.7 Hz, 1H), 3.85 (s, 3H), 2.99 – 2.85 (m, 1H), 2.77 – 2.66 (m, 2H), 2.44 (ddd, *J* = 16.9, 8.1, 4.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3, 160.1, 148.5, 131.3, 127.3, 122.5, 114.3, 72.8, 55.3, 29.7, 27.5; HRMS (ESI+) calcd. for: $C_{13}H_{14}N_4NaO_2$ 281.1014. (M+ H), found 281.1003.

1-methyl-5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrrolidin-2-one [10] (5d, Table 3)

TLC R_f=0.3 **(**60% EtOAc/Hexane**)**; Yield 91% (55 mg); Colorless liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.83 – 7.75 (m, 2H), 7.41 (t, *J* = 8 Hz, 2H), 7.38 (m, 1H), 6.05 (dd, *J* = 7.5, 1.3 Hz, 1H), 3.03 – 2.89 (m, 1H), 2.75 (s, 3H), 2.70 – 2.41 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 148.6, 131.9, 129.8, 128.9, 128.8, 126.0, 78.8, 28.9, 27.6, 25.2; HRMS (ESI+) calcd. for: $C_{13}H_{15}N_4O$ 243.1246. (M+ H), found 243.1251.

5-(4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)-1-methylpyrrolidin-2-one and 1-((4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidin-2-one (5e and 5e', Table 3)

TLC R_f=0.3 **(**60% EtOAc/Hexane**)**; Yield 62% (40 mg); Colorless liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 6.8 Hz, 2H), 7.77 (ddd, *J* = 6.6, 4.3, 1.1 Hz, 3H), 7.18 – 7.05 (m, 3H), 6.04 (dd, *J* = 7.5, 1.6 Hz, 1H), 5.85 (s, 1H), 3.53 – 3.43 (m, 1H), 3.03 – 2.87 (m, 1H), 2.74 (s, 3H), 2.68 – 2.56 (m, 2H), 2.5 (m, 4H), 2.11 – 1.98 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 175.4, 163.0 (d, J_{C-F} = 246.2 Hz), 163.0 (d, J_{C-F} = 247.4 Hz, **5e'**), 147.8, 147.7, 131.7, 131.6, 127.8, 127.7, 126.1, 126.0, 116.0 (d, J_{C-F} = 21.2 Hz), 115.9 (d, J_{C-F} = 21.2 Hz, **5e'**), 78.9, 60.0, 46.2, 30.5, 28.9, 27.6, 25.2, 17.7; HRMS (ESI+) calcd. for: $C_{13}H_{14}FN_4O$ 261.1152. (M+ H), found 261.1151.

5-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-1-methylpyrrolidin-2-one and 1-((4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidin-2-one (5f and 5f', Table 3)

TLC R_f=0.3 **(**60% EtOAc/Hexane**)**; Yield 52% (34.5 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.81 (s, 1H), 7.73 (t, *J* = 2.2 Hz, 1H), 7.71 (t, *J* = 2.2 Hz, 1H), 6.97 (d, *J* = 3.6 Hz, 1H), 6.96 – 6.94 (m, 1H), 6.02 (dd, *J* = 7.5, 1.7 Hz, 1H), 5.84 (s, 1H), 3.85 (s, 1H), 3.85 (s, 1H), 3.47 (dd, *J* = 8.9, 5.3 Hz, 1H), 3.02 – 2.87 (m, 1H), 2.74 (s, 1H), 2.67 – 2.58 (m, 1H), 2.52 (ddd, *J* = 10.9, 4.8, 2.8 Hz, 1H), 2.49 – 2.41 (m, 1H), 2.04 (dt, *J* = 11.3, 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 175.3, 160.0, 160.0, 148.6, 148.4, 131.5, 131.3, 127.4, 127.3, 122.7, 122.5, 114.3, 114.3, 78.7, 59.9, 55.3, 46.2, 30.5, 28.9, 25.2, 17.7.; HRMS (ESI+) calcd. for: $C_{14}H_{17}N_4O_2$ 273.1352. (M+ H), found 273.1347.

***N*-methyl-*N*-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)acetamide (5g, Table 3)**

TLC R_f=0.2 **(**50% EtOAc/Hexane**)**; Yield 69% (40 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of rotamers) δ 7.82 (s, 1H), 7.72 (t, *J* = 6.4 Hz, 1H), 7.37 (dd, *J* = 13.8, 6.9 Hz, 2H), 7.33 – 7.27 (m, 2H), 5.9, 5.7 (2Xs, 2X2H), 3.05, 2.99 (2Xs, 2X3H), 2.40, 2.10 (2Xs, 2X3H).^{13}C NMR (126 MHz, $CDCl_3$): (mixture of rotamers) δ 170.4, 147.7, 147.3, 130.9, 130.8, 129, 128.7, 127.9, 127.8, 127.6, 125.0, 124.9, 66.8, 62.6, 34.2, 32.2, 28.6, 20.7; HRMS (ESI+) calcd. for: $C_{12}H_{15}N_4O$ 231.1242. (M+ H), found 231.1225.

***N*-((4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*-methylacetamide (5h, Table 3)**

TLC R_f=0.2 **(**50% EtOAc/Hexane**)**; Yield 59% (38 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of rotamers) δ 7.84 (d, *J* = 2.8 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.12 (dd, *J* = 15.7, 8.6 Hz, 2H), 5.96, 5.83 (2Xs, 2X2H), 3.13, 3.06 (2Xs, 2X3H), 2.47, 2.17 (2Xs, 2X3H); ^{13}C NMR (101 MHz, $CDCl_3$): (mixture of rotamers) δ 170.5, 170.4, 163 (d, $J_{(C\text{-}F)}$ = 308.7 Hz), 161.9 ($J_{(C\text{-}F)}$ = 307.5 Hz), 146.9, 146.5, 130.7, 130.5, 126.8, 126.7, 115.0, 114.9, 114.8, 114.7, 66.8, 62.7, 34.3, 32.2, 20.7, 20.6; HRMS (ESI+) calcd. for: $C_{12}H_{14}FN_4O$ 249.1152. (M+ H), found 249.1142.

***N*-((4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*-methylacetamide (5i, Table 3)**

TLC R_f=0.2 **(**50% EtOAc/Hexane**)**; Yield 52% (32 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of rotamers) δ 7.81 (s, 1H), 7.74 – 7.69 (m, 2H), 6.99 – 6.94 (m, 2H), 5.95, 5.81 (2Xs, 2X2H), 3.85 (2Xs, 2X3H), 3.11, 3.05 (2Xs, 2X3H), 2.47, 2.17 (2Xs, 2X3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (mixture of rotamers) 171.4, 160.0, 159.9, 148.6, 131.4, 131.4, 127.3, 127.3, 122.7, 122.4, 114.3, 114.3, 67.7, 63.5, 55.3, 35.2, 33.2, 29.7, 21.8, 21.7; HRMS (ESI+) calcd. for: $C_{13}H_{17}N_4O_2$ 261.1352. (M+ H), found 261.1346.

1-methyl-5-(1*H*-1,2,3-triazol-1-yl)pyrrolidin-2-one (5k, Table 3)

TLC R_f=0.3 **(**60% EtOAc/Hexane**)**; Yield 82% (34 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 2H), 6.07 (d, *J* = 7.5 Hz, 1H), 2.92 (dt, *J* = 18.1, 9.2 Hz, 1H), 2.69 (s, 3H), 2.66 – 2.41 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 135.0, 78.6, 28.8, 27.4, 25.0; HRMS (ESI+) calcd. for: $C_7H_{11}N_4O$ 167.0933. (M+ H), found 167.0947.

5-(1*H*-1,2,3-triazol-1-yl)pyrrolidin-2-one (5l, Table 3)

TLC R_f=0.2 **(**60% EtOAc/Hexane**)**; Yield 62%; Colorless liquid (23 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (broad, 1H), 7.65 (d, *J* = 17.8 Hz, 2H), 6.20 (d, *J* = 6.9 Hz, 1H), 2.93 – 2.76 (m, 1H), 2.76 – 2.50 (m, 2H), 2.39 (dd, *J* = 16.4, 9.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.9, 134.9, 73.0, 28.4, 27.4; HRMS (ESI+) calcd. for: $C_6H_9N_4O$ 153.0776. (M+ H), found 153.0779

***N*-((1*H*-1,2,4-triazol-1-yl)methyl)-*N*-methylacetamide (5m, Table 3)**

TLC R_f=0.5 **(**5% MeOH/DCM**)**; Yield 54%; Colorless liquid (21 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.92 (s, 1H), 5.64 (s, 2H), 3.20 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 151.6, 144.4, 59.5, 36.3, 21.6; HRMS (ESI+) calcd. for: $C_6H_{11}N_4O$ 155.0933. (M+ H), found 155.0939.

1-methyl-5-(1*H*-1,2,4-triazol-1-yl)pyrrolidin-2-one (5n, Table 3)

TLC R_f=0.5 **(**5% MeOH/DCM**)**; Yield 73% (30 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.02 (s, 1H), 5.83 (dd, *J* = 7.8, 1.7 Hz, 1H), 2.86 (dd, *J* = 16.1, 7.8 Hz, 1H), 2.71 (s, 3H), 2.58 (m, 2H), 2.36 (ddd, *J* = 15.4, 7.2, 2.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 153.1, 142.4, 74.5, 28.7, 27.3, 25.6; HRMS (ESI+) calcd. for: $C_7H_{11}N_4O$ 167.0933. (M+ H), found 167.0944.

***N*-methyl-*N*-((5-phenyl-2*H*-tetrazol-2-yl)methyl)acetamide (5o, Table 3)**

TLC R_f=0.6 **(**5% MeOH/DCM**)**; Yield 62%; Colorless liquid (36 mg); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers): δ 8.22 – 8.08 (m, 2H), 7.54 – 7.39 (m, 3H), 6.17, 6.07 (2Xs, 2X2H), 3.19, 3.08 (2Xs, 2X3H), 2.48, 2.18 (2Xs, 2X3H); ^{13}C NMR (126 MHz, $CDCl_3$) (mixture of rotamers): δ 171.6, 171.2, 165.7, 165.4, 130.7, 130.5, 129.0, 128.8, 127.0, 126.9, 126.9, 126.8, 66.3, 62.3, 35.7, 33.3, 21.7, 21.6; HRMS (ESI+) calcd. for: $C_{11}H_{13}N_5NaO$ 254.1018. (M+ Na), found 254.1019.

***N*-((1*H*-benzo[*d*]imidazol-1-yl)methyl)-*N*-methylacetamide [9] (7a, Table 4)**

TLC R_f=0.6 **(**5% MeOH/DCM**)**; Yield 52% (26 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.81 (d, *J* = 6.2 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.32 (dd, *J* = 9.7, 5.4 Hz, 2H), 5.75 (s, 2H), 3.01 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 143.5,

133.2, 123.6, 122.6, 120.2, 110.3, 55.1, 35.0, 21.8; HRMS (ESI+) calcd. for: $C_{11}H_{14}N_3O$ 204.1137. (M+ H), found 204.1128.

_N_-((6-bromo-1_H_-benzo[_d_]imidazol-1-yl)methyl)-_N_-methylacetamide and _N_-((5-bromo-1_H_-benzo[_d_]imidazol-1-yl)methyl)-_N_-methylacetamide (7b and 7b', Table 4)

TLC R_f=0.6 **(**5% MeOH/DCM**)**; Yield 56% (39 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 3.2 Hz, 2H), 7.94 (d, *J* = 1.3 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.41 (ddd, *J* = 8.6, 3.0, 1.8 Hz, 1H), 5.72 (s, 2H), 5.69 (s, 2H), 3.05 (s, 3H), 3.02 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 171.6, 144.9, 144.4, 144.2, 142.5, 134.4, 132.2, 126.7, 126.1, 126.0, 123.1, 121.5, 117.0, 115.8, 113.4, 111.8, 55.3, 35.3, 35.0, 21.8; HRMS (ESI+) calcd. for: $C_{11}H_{13}BrN_3O$ 282.0242. (M+ H), found 282.0241.

_N_-((5,6-dimethyl-1_H_-benzo[_d_]imidazol-1-yl)methyl)-_N_-methylacetamide (7c, Table 4)

TLC R_f=0.6 **(**5% MeOH/DCM**)**; Yield 52% (30 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.56 (s, 1H), 7.33 (s, 1H), 5.69 (s, 2H), 2.99 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H), 2.13 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 142.8, 142.2, 132.8, 131.7, 131.6, 120.3, 110.3, 54.9, 34.8, 21.9, 20.6, 20.2; HRMS (ESI+) calcd. for: $C_{13}H_{18}N_3O$ 232.1450. (M+ H), found 232.1459.

1-methyl-5-(3-phenyl-1_H_-pyrazol-1-yl)pyrrolidin-2-one (7g, Table 4)

TLC R_f=0.3 **(**60% EtOAc/Hexane**)**; Yield 58% (34 mg); Yellow color liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 2.3 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 5.65 (dd, *J* = 7.7, 2.2 Hz, 1H), 2.85 – 2.72 (m, 1H), 2.64 (s, 3H), 2.55 – 2.45 (m, 2H), 2.36 – 2.23 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 152.6, 133.0, 128.7, 128.6, 127.9, 125.6, 103.6, 76.5, 29.1, 27.3, 25.9; HRMS (ESI+) calcd. for: $C_{14}H_{15}N_3ONa$ 264.1113. (M+ Na), found 264.1116.

5-(3-(4-bromophenyl)-1_H_-pyrazol-1-yl)-1-methylpyrrolidin-2-one (7h, Table 4)

TLC R_f=0.3 **(**60% EtOAc/Hexane**)**; Yield 59% (47 mg); Yellow color liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.55 (m, 2H), 7.48 – 7.36 (m, 2H), 7.19 (s, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 5.65 (dd, *J* = 7.7, 2.3 Hz, 1H), 2.84 – 2.72 (m, 1H), 2.66 (s, 3H), 2.56 – 2.39 (m, 2H), 2.34 – 2.25 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 151.5, 131.9, 131.7, 128.9, 127.2, 121.9, 103.6, 76.6, 29.0, 27.4, 26.0; HRMS (ESI+) calcd. for: $C_{14}H_{15}BrN_3O$ 320.0398. (M+H), found 320.0389.

5-(3-(4-bromophenyl)-1*H*-pyrazol-1-yl)pyrrolidin-2-one (7i, Table 4)

TLC R_f=0.2 **(**60% EtOAc/Hexane**)**; Yield 56% (42 mg); White solid; m.p.: 156-158 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 6.7, 1.8 Hz, 2H), 7.50 (dd, *J* = 6.7, 1.9 Hz, 3H), 7.25 (s, 1H), 6.89 (s, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 5.89 (d, *J* = 7.4 Hz, 1H), 2.88 – 2.56 (m, 1H), 2.56 – 2.27 (m, 2H); ^{13}C NMR (126 MH , $CDCl_3$) δ 178.2, 151.5, 132.0, 131.7, 128.3, 127.2, 121.9, 103.6, 70.7, 29.7, 28.5; HRMS (ESI+) calcd. for: $C_{13}H_{13}BrN_3O$ 306.0242. (M+ H), found 306.0245.

***N*-(1-methyl-5-oxopyrrolidin-2-yl)benzamide [13] (9b, Table 5)**

TLC R_f=0.5 **(**5% MeOH/DCM**)**; Yield 61% (33 mg); White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.4 Hz, 2H), 7.76 (s, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 5.84 – 5.72 (m, 1H), 2.73 (s, 3H), 2.50 – 2.35 (m, 2H), 2.32 – 2.20 (m, 1H), 1.96 – 1.84 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 167.5, 133.4, 131.9, 128.5, 127.3, 66.0, 29.3, 27.3, 25.8; HRMS (ESI+) calcd. for: $C_{12}H_{15}N_2O_2$ 219.1134. (M+ H), found 219.1138.

4-methyl-*N*-(1-methyl-5-oxopyrrolidin-2-yl)benzamide [13] (9d, Table 5)

TLC R_f=0.5 **(**5% MeOH/DCM**)**; Yield 57% (33 mg); White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.79 (td, *J* = 8.8, 3.4 Hz, 1H), 2.73 (s, 3H), 2.50 – 2.36 (m, 2H), 2.32 (s, 3H), 2.07 (dd, *J* = 14.1, 6.9 Hz, 1H), 1.94 – 1.83 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 167.4, 142.5, 130.4, 129.2, 127.3, 65.9, 29.3, 27.3, 25.8, 21.5; HRMS (ESI+) calcd. for: $C_{13}H_{17}N_2O_2$ 233.1290. (M+ H), found 233.1303.

3-methyl-*N*-(1-methyl-5-oxopyrrolidin-2-yl)benzamide [13] (9e, Table 5)

TLC R_f=0.5 **(**5% MeOH/DCM); Yield 52% (30 mg); Colorless liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.61 (m, 2H), 7.46 (s, 1H), 7.33 (d, *J* = 6.1 Hz, 2H), 5.86 (td, *J* = 8.7, 3.6 Hz, 1H), 2.82 (s, 3H), 2.60 – 2.45 (m, 2H), 2.43 – 2.29 (m, 4H), 2.03 – 1.85 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 167.6, 138.5, 133.3, 132.7, 128.4, 128.0, 124.2, 65.9, 29.2, 27.3, 25.9, 21.3; HRMS (ESI+) calcd. for: $C_{13}H_{17}N_2O_2$ 233.1290. (M+ H), found 233.1303.

***N*-(1-methyl-5-oxopyrrolidin-2-yl)-4-nitrobenzamide [13] (9f, Table 5)**

TLC R_f=0.5 **(**5% MeOH/DCM**)**; Yield 32% (21 mg); White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.9 Hz, 2H), 8.08 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 1H), 5.83 (td, *J* = 8.7, 2.8 Hz, 1H), 2.79 (s, 2H), 2.56 – 2.18 (m, 4H), 1.93 (tdd, *J* = 10.7, 6.1, 3.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 165.2, 149.9, 138.7, 128.6, 123.8, 66.5, 29.2, 27.6, 25.9; HRMS (ESI+) calcd. for: $C_{12}H_{14}N_3O_4$ 264.0984. (M+ H), found 264.0989.

3-fluoro-*N*-(1-methyl-5-oxopyrrolidin-2-yl)benzamide [13] (9g, Table 5)

TLC R_f=0.5 **(**5% MeOH/DCM); Yield 54% (31 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.96 (td, *J* = 7.8, 1.6 Hz, 1H), 7.44 (dd, *J* = 14.3, 6.5 Hz, 1H), 7.21 (t, *J* = 11.2 Hz, 1H), 7.13 – 6.94 (m, 2H), 5.78 (dt, *J* = 11.4, 5.5 Hz, 1H), 2.78 (s, 3H), 2.54 – 2.41 (m, 2H), 2.40 – 2.24 (m, 1H), 1.91 – 1.79 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 162.5, 160.5 (d, $J_{(C-F)}$ = 248.2 Hz), 133.9 (d, $J_{(C-F)}$ = 8.7 Hz) 131.9, 124.9, 120.5, 116.1 (d, $J_{(C-F)}$ = 25 Hz), 65.8, 29.1, 27.3, 26.1; HRMS (ESI+) calcd. for: $C_{12}H_{14}FN_2O_2$ 237.1039. (M+H), found 237.1049.

4-methyl-*N*-(1-methyl-5-oxopyrrolidin-2-ylidene)benzenesulfonamide (9h, Table 5)

TLC R_f=0.5 **(**40% EtOAc/Hexane); Yield 61% (40 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 3.36 – 3.26 (m, 2H), 2.96 (s, 3H), 2.68 – 2.61 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 172.6, 143.6, 138.3, 129.5, 126.9, 27.9, 26.6, 26.3, 21.5; HRMS (ESI+) calcd. for: $C_{12}H_{15}N_2O_3S$ 267.0803. (M+H), found 267.0806.

Procedure for the synthesis of compound 10 (Fig. 3):

In a 25 ml round bottom flask with magnetic bar, compound **3d** (0.13 mmol) was dissolved in 5 ml of dry DCM under N_2 atmosphere. Phenol (0.13 mmol) was added followed by the addition of 0.26 mmol anhydrous $AlCl_3$. Reaction mixture was allowed to reflux at 40 ^{o}C and progress of reaction was monitored by TLC. After completion of reaction, solvent was evaporated and neutralized crude product with saturated $NaHCO_3$ solution. Required product **10** was purified on column chromatography (100-200 mesh size) using EtOAc and hexane (2:8) as eluents.

Spectral data of *N*-(2-hydroxybenzyl)-*N*-methylbenzamide (10, Fig. 3)

TLC R_f=0.5 **(**20% EtOAc/Hexane**)**; Yield 64% (20 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.39 (m, 2H), 7.34 (m, 3H), 7.24-7.15 (m, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.76 (t, *J* = 7.3 Hz, 1H), 4.54 (s, 2H), 2.96 (s, 3H);^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 156.4, 134.2, 131.9, 130.6, 130.5, 128.4, 127.7, 121.2, 119.2, 117.7, 49.1, 37.1; HRMS (ESI+) calcd. for: $C_{15}H_{16}NO_2$ 242.1181. (M+ H), found 242.1186.

Procedure for the synthesis compound 11 (Fig. 3):

In a 50 ml round bottom flask with magnetic bar, compound **3i** (0.37 mmol) was dissolved in 8 ml of methanol. 1*H*-indole (0.37 mmol) was added to the reaction mixture. Con. HCl (0.7 ml) in 2 ml of water was added. Reaction mixture was refluxed and progress of the reaction was monitored by TLC. After completion of reaction, solvent was evaporated and neutralized crude

product with saturated $NaHCO_3$ solution. Required product **11** was purified on column chromatography (100-200 size) using EtOAc and hexane (70:30) as eluents.

Spectral data of 5-(1*H*-indol-3-yl)-1-methylpyrrolidin-2-one [14] (11, Fig. 3)

TLC R_f=0.2 **(**70% EtOAc/Hexane**)**; Yield 82% (65 mg); Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.07 – 6.99 (m, 2H), 4.79 (t, *J* = 7.2 Hz, 1H), 2.62 (s, 3H), 2.59 – 2.53 (m, 1H), 2.51 – 2.32 (m, 2H), 2.18 – 2.07 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 137.0, 125.2, 122.9, 122.4, 119.8, 118.7, 114.8, 111.8, 58.0, 30.8, 28.1, 26.9; HRMS (ESI+) calcd. for: $C_{13}H_{15}N_2O$ 215.1184 (M+ H), found 215.1167.

Procedure for the synthesis of compound 12 (Fig. 3):

In a 50 ml round bottom flask with magnetic bar, compound **3i** (0.37 mmol) was dissolved in 8 ml of methanol. Trimethoxy benzene (0.37 mmol) was added to the reaction mixture. Con. HCl (0.7 ml) in 2 ml of water was added. Reaction mixture was refluxed and progress of the reaction was monitored by TLC. After completion of reaction, solvent was evaporated and neutralized crude product with saturated $NaHCO_3$ solution. Required product **12** was purified on column chromatography (100-200 mesh size) using EtOAc and hexane (60:40) solvents.

Spectral data of 1-methyl-5-(2,4,6-trimethoxyphenyl)pyrrolidin-2-one [15] (12, Fig. 3)

TLC R_f=0.3 (70% EtOAc/Hexane); Yield 85% (82 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (d, *J* = 8.0 Hz, 2H), 5.16 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 6H), 2.58 – 2.50 (m, 1H), 2.47 (s, 3H), 2.43 – 2.32 (m, 2H), 2.24 (dt, *J* = 16.5, 11.4 Hz, 1H), 2.02 – 1.87 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 160.9, 108.1, 55.8, 55.3, 54.2, 31.1, 27.5, 23.7; HRMS (ESI+) calcd. for: $C_{14}H_{20}NO_4$ 266.1392 (M+ H), found 266.1394.

Procedures for the free radical scavenger experiments with TEMPO (Fig. 3, eq. 1, 2 and 3):

To a 100 ml sealed tube with magnetic bar, azole **1** (0.25 mmol) and amide **2** (1 mmol) was loaded. Free radical scavenger TEMPO (0.5 mmol and 1.5 mmol) was added to the reaction mixture. *tert*-Butylhydroperoxide (5-6 M in Decane) 0.75 mmol was added followed by the addition of tetrabutylammonium iodide (0.025 mmol). Reaction mixture was allowed to stir at 110 ^{o}C. Progress of reaction was monitored by TLC. After completion of reaction, required products **13** and **14** were isolated on column chromatography (100-200 mesh size) using EtOAc and hexane (40:60) solvents.

Spectral data of *N*-methyl-*N*-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)acetamide[16] (13) (eq. 1, Fig. 4)

TLC R_f=0.5 **(**40% EtOAc/Hexane**)**; Yellow liquid. Yield 73% (90 mg, when 0.5 mmol of TEMPO was taken, yield was calculated with respect to TEMPO). Yield 96% (220 mg, when 1.25 mmol of TEMPO was taken, yield was calculated with respect to DMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (s, 2H), 2.97 (s, 3H), 2.15 (s, 3H), 1.40 (s, 6H), 1.1 (m, 6H), 1.04 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 85.5, 60.0, 39.8, 34.1, 33.1, 29.7, 22.1, 21.5, 20.0, 17.0; HRMS (ESI+) calcd for: $C_{13}H_{27}N_2O_2$ 243.2073. (M+H), found 243.2075.

Spectral data of 1-methyl-5-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (14) (eq. 3, Fig. 4)

TLC R_f=0.5 (40% EtOAc/Hexane); Yellow liquid. Yield 62%. (78 mg, when 0.5 mmol of TEMPO was taken, yield was calculated with respect to TEMPO); Yield 65%. (81 mg, when 1.25 mmol of TEMPO was taken, yield was calculated with respect to TEMPO); Yield 80% (208 mg, when 1.25 mmol of TEMPO was taken, yield was calculated with respect to NMP); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (d, J = 6.0 Hz, 1H), 3.08 (s, 3H), 2.57 (dt, J = 17.6, 9.0 Hz, 1H), 2.33 – 2.20 (m, 2H), 2.14 – 1.96 (m, 1H), 1.45 (d, J = 11.6 Hz, 6H), 1.37-1.14 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 93.6, 60.3, 60.0, 59.7, 40.1, 39.6, 34.2, 32.7, 30.8, 29.0, 25.8, 20.3, 20.2, 17.1; HRMS (ESI+) calcd. for: $C_{14}H_{27}N_2O_2$ 255.2073. (M+ H), found 255.2078.

Procedures for the free radical scavenger experiments with 1,1-diphenylethylene (DPE) (Fig. 4, eq. 4 to eq. 12):

To a 100 ml sealed tube with magnetic bar, azole **1**, **4**, and **6** (0.25 mmol) and amide (1 mmol) was loaded. Free radical scavenger 1,1-diphenylethylene (0.5 mmol) was added to the reaction mixture. *tert*-Butylhydroperoxide (5-6 M in Decane) 0.75 mmol was added followed by the addition of tetrabutylammonium iodide (0.025 mmol). Reaction mixture was allowed to stir at 110 ^{o}C. Progress of the reaction was monitored by TLC. After completion of reaction, required products **15**, **16**, **17**and **19** were isolated on column chromatography (100-200 mesh size) using EtOAc and hexane (20:80) as eluents. Compound **18** was isolated on column chromatography (100-200 mesh size) using MeOH and DCM (2:98) as eluents.

Spectral data of 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-1,1-diphenylethan-1-ol (15) (Eq. 4, 5, Fig. 4)

TLC R_f=0.5 **(**30% EtOAc/Hexane**)**; Yield 72% (56 mg, yield was calculated based on the 1*H*-benzotriazole); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.21– 7.06 (m, 11H), 5.23 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 143.4, 134.0, 128.4, 127.7, 127.5, 127.4, 126.4, 126.2, 123.9, 119.8, 109.7, 78.5, 57.3; HRMS (ESI+) calcd. for: $C_{20}H_{18}N_3O$ 316.1450. (M+ H), found 316.1455.

Spectral data of 1,1-diphenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1-ol (16) (Eq. 6, Fig. 4)

TLC R_f=0.6 **(**30% EtOAc/Hexane**)**; Yield 75% (63 mg, yield was calculated based on the 4-phenyl-1*H*-1,2,3-triazole); White solid; m.p.: 180-181 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 2H), 7.53 (s, 1H), 7.47 – 7.43 (m, 5H), 7.41 – 7.27 (m, 9H), 5.15 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 143.0, 130.3, 128.8, 128.5, 128.4, 128.1, 127.9, 126.4, 126.1, 125.6, 121.3, 59.5; HRMS (ESI+) calcd. for: $C_{22}H_{20}N_3O$ 342.1606. (M+ H), found 342.1610.

Spectral data of 1,1-diphenyl-2-(5-phenyl-2*H*-tetrazol-2-yl)ethan-1-ol (17) (Eq. 9, Fig. 4)

TLC R_f=0.6 **(**20% EtOAc/Hexane**)**; Yield 75% (53 mg, yield was calculated based on the 5-phenyl-1*H*-tetrazole) Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (ddd, *J* = 8.2, 4.0, 2.3 Hz, 2H), 7.44 – 7.38 (m, 3H), 7.31 – 7.26 (m, 6H), 7.12 (ddd, *J* = 5.1, 3.9, 2.0 Hz, 5H), 4.76 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 139.1, 130.6, 128.9, 128.6, 128.4, 128.2, 127.0, 126.9, 78.7, 69.1; HRMS (ESI+) calcd for: $C_{21}H_{19}N_4O$ 343.1559. (M+ H), found 343.1561.

Spectral data of 2-(1*H*-benzo[*d*]imidazol-1-yl)-1,1-diphenylethan-1-ol (18) (Eq. 10, Fig. 4,)

TLC R_f=0.5 (5% MeOH/DCM); Yield 42% (32 mg, yield was calculated based on the 1*H*-benzimidazole); White solid; m.p.:171-173 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.5 Hz, 1H), 7.43 (s, 1H), 7.35 – 7.19 (m, 10H), 7.17 – 7.06 (m, 4H), 4.86 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 128.9, 128.5, 127.8, 126.2, 122.7, 121.8, 119.6, 110.0, 78.2, 54.7; HRMS (ESI+) calcd. for: $C_{21}H_{19}N_2O$ 315.1497. (M+ H), found 315.1493.

Spectral data of 2-(3-(4-bromophenyl)-1*H*-pyrazol-1-yl)-1,1-diphenylethan-1-ol (19) (Eq. 11, Fig. 4)

TLC R_f=0.5 (40% EtOAc/Hexane); Yield 12% (13 mg, yield was calculated based on the 1*H*-(3-(4-bromophenyl)-1*H*-pyrazole); White solid; m.p.:193-195 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 2H), 7.47 – 7.35 (m, 6H), 7.24 (t, *J* = 7.4 Hz, 4H), 7.16 (ddd, *J* = 8.5, 2.5, 1.3 Hz, 2H), 7.11 (d, *J* = 2.3 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 6.07 (s, 1H), 4.77 (s, 2H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 150.9, 143.8, 132.8, 131.7, 128.3, 128.2, 127.6, 127.3, 127.1, 126.1, 102.4, 78.3, 60.3; HRMS (ESI+) calcd. for: $C_{23}H_{20}BrN_2O$ 419.0759. (M+ H), found 419.0761.

Procedure for the synthesis of compounds 21 (Table 6):

To a 50 ml round bottom flask with magnetic bar, azole **1** (0.25 mmol) and 1*H*-indole **22** (0.25 mmol) was dissolved in 6 ml of DCE solvent. *tert*-Butylhydroperoxide (70% in water) 0.75 mmol was added followed by the addition of tetrabutylammonium iodide (0.025 mmol). Reaction mixture was allowed to stir at 80 ^oC. Progress of reaction was monitored by TLC. After completion of reaction, required product **21** was obtained on column chromatography (100-200 mesh size) using EtOAc and hexane (15:85) as eluent

Spectral data of 1-(1*H*-indol-2-yl)-1*H*-benzo[*d*][1,2,3]triazole [17] (21, Table 6)

TLC R_f=0.5 (20% EtOAc/Hexane**)**; Yield 45% (26 mg); White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.52 – 7.47 (m, 2H), 7.33 – 7.28 (m, 1H), 6.81 – 6.80 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.3, 133.6, 131.4, 131.2, 129.0, 127.0, 125.1, 123.3, 121.1, 120.9, 120.5, 111.3, 110.8, 90.9. HRMS (ESI+) calcd. for: $C_{14}H_{11}N_4$ 235.0984. (M+ H), found 235.0992.

General procedure for the synthesis of un/substituted *N, N*-dimethylbenzamides (2):

In a 100 ml round bottom flask with magnetic bar, 1 g of benzoyl chloride was dissolved in 20 ml THF. *N, N*-dimethylamine (3 ml) was added slowly to the reaction mixture at room temperature. Reaction was allowed to stir at room temperature for 6 h. Reaction was monitored by TLC and required product was isolated on column chromatography (60-120 mesh size) using EtOAc and hexane solvents.

General procedure for the synthesis of 4-aryl-*NH*-1,2,3-triazoles (4):

4-aryl-*NH*-1,2,3-triazoles were synthesized by known procedure.[18] In a 100 ml round bottom flask with magnetic bar, nitro olefin (0.3 mmol) and NaN_3 (0.45 mmol) were dissolved in 8 ml DMF, then PTSA (0.15 mmol) was added. Reaction mixture was allowed to stir at 60 ^oC for 1 h. Compound was purified on column chromatography using EtOAc and hexane solvents.

General procedure for the synthesis of 5-phenyl-1*H*-tetrazole (4):

4-aryl-*NH*-1,2,3-triazoles were synthesised by known procedure.[19] To a 100 ml round bottom flask with magnetic bar, equipped with N_2 balloon, benzonitrile (1 mmol) was dissolved in 10 ml of dry DMF. NaN_3 (1.5 mmol) was added at room temperature and reaction was stirred

at 120 ^{0}C for 12 h. After completing reaction, reaction mixture was allowed to cool at room temperature and dissolved in 30 ml of cold water. Product was obtained by precipitation; solid product was dried *in vaccuo* and used without further purification.

ASSOCIATED CONTENT

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Note

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SUPPORTING INFORMATION

Supporting information contains XRD-data and spectra of all compounds.

REFERENCES

1. Metal catalyzed C-H activation reactions: a) Chen, X.; Engle, K, M.; Wang, D, H.; Yu, J, Q. *Angew. Chem., Int. Ed.,* **2009**, *48*, 5094. b) Sun, C, L.; Li, B. J.; Shi, Z, J. *Chem. Rev.,* **2011**, *111*, 1293. c) Guo, X, X.; Gu, D. W.; wu, Z.; Zhang, W. *Chem. Rev.,* **2015**, *115*, 1622. d) Moselage, M.; Li, J.; Auckermann, L. *ACS Catal.,* **2016**, *6*, 498.

2. Metal free C-H activation reactions: a) Pan, S, C. *Beilsteein J. Org. Chem.,* **2012**, *8*, 1374. b) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C.; *Chem. Commun.,* **2012**, *48*, 979. c) Zhou, M, B.; song, R. J.; Ouyang, X. U.; Liu, Y.; Wei, W. T.; Deng, G. B.; Lei. J. H.; *Chem. Sci.,* **2013**, *4*, 2690.

3. (a) Wu, X.-F.; Gong, J.-L.; Qi, X. *Org. Biomol. Chem.* **2014**, *12*, 5807. (b) Jia, Z.; Nagano, T.; Li, X.; Chan, A. S. C. *Eur. J. Org. Chem.,* **2013**, *2013*, 858. c) Nobuta, T.; Tada, N.; Fujiya, A.; Kariya, A.; Miura, T.; Itoh, A. *Org. Lett.,* **2013**, *15*, 574.

4. C-N bond formation: (a) Zhao, J.; Li, P.; Xia, C.; Li, F. *Chem. Commun.* **2014**, *50*, 4751. (b) Yuan, Y.; Hou, W.; Zhang-Negrerie, D.; Zhao, K.; Du, Y. *Org. Lett.* **2014**, *16*, 5410. (c) Majji, G.; Rajamanickam, S.; Khatun, N.; Santra, S. K.; Patel, B. K. *J. Org. Chem.* **2015**, *80*, 3440 (d) Lv, Y.; Li, Y.; Xiong, T.; Lu, Y.; Liu, Q.; Zhang, Q. *Chem. Commun.*

2014, *50*, 2367. (e) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 3231. (f) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979. (g) Xue, Q.; Xie, J.; Xu, P.; Hu, K.; Cheng, Y.; Zhu, C. *ACS Catal.,* **2013**, *3*, 1365.

5. C-O bond formation: (a) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem. Eur. J.* **2011**, *17*, 4085. (b) Zhang, S.; Guo, L. N.; Wang, H.; Duan, X. H. *Org. Biomol. Chem.* **2013**, *11*, 4308. (c) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331. (d) Guo, S.; Yu, J. T.; Dai, Q.; Yang, H.; Cheng, J. *Chem. Commun.* **2014**, *50*, 6240. (e) Xu, W.; Nachtsheim, B. J. *Org. Lett.* **2015**, *17*, 1585. (f) Shi, E.; Shao, Y.; Chen, S.; Hu, H.; Liu, Z.; Zhang, J.; Wan, X. *Org. Lett.* **2012**, *14*, 3384.

6. C-S bond formation: (a) Xiao, F.; Chen, H.; Xie, H.; Chen, S.; Yang, L.; Deng, G.-J. *Org. Lett.* **2014**, *16*, 50. (b) Gao, W.-C.; Zhao, J.-J.; Chang, H.-H.; Li, X.; Liu, Q.; Wei, W.-L. *RSC Adv.* **2014**, *4*, 49329. (c) Zhang, J.; Shao, Y.; Wang, H.; Luo, Q.; Chen, J.; Xu, D.; Wan, X. *Org. Lett.* **2014**, *16*, 3312. (d) Li, X.; Xu, X.; Zhou, C. *Chem. Commun.* **2012**, *48*, 12240.

7. Aruri, H.; Singh, U.; Sharma, S.; Gudup, S.; Bhogal, M.; Kumar, S.; Singh, D.; Gupta, V. K.; Kant, R.; Vishwakarma, R. A.; Singh, P. P. *J. Org. Chem.* **2015**, *80*, 1929.

8. 8. a) N. Siddiqui, M. S. Alam, W. Ahsan, *Acta Pharma.* **2008**, *58*, 445. b) M.I. Hegab, A. S.M. Abdel-Fattah, N. M. Yousef, *Archiv der Pharmazie, Chemistry in Life Sciences* **2007**, *340*, 396.

9. Q. Xia, W. Chen, *J. Org. Chem.,* **2012**, 77, 9366.

10. Singh, M. K.; Akula, H. K.; Satishkumar, S.; Stahl, L.; Lakshman, M. K. *ACS Catal*. **2016**, *6*, 1921.

11. (a) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.,* **1998**, *98*, 409. (b) Katritzky, A. R.; Rachwal, S. *Chem. Rev.,* **2010**, *110*, 1564.

12. Katritzky, A. R.; Yao, G.; Lan, X.; Zhao, X. *J. Org. Chem.* **1993**, *58*, 2086.

13. Mao, X.; Wu, Y.; Jang, X.; Liu, X.; Cheng, Y.; Zhu, C. *RSC Adv.,* **2012**, *2*, 6733.

14. Priyadarshini, S.; Amal Joseph, P.J.; Kantam, M.L. *Tetrahedron* **2014**, *70*, 6068.

15. Shikarawa, E.; Uchiyama, N.; Hayashi, T. *J. Org. Chem.* **2011**, *76*, 25.

16. Lao, Q-J.; Zhong, W-H.; Lou, Q-H.; Li, Z-J.; Meng, X-B. *Org. Biomol. Chem.,* **2012**, *10*, 7869.

17. Beukeaw, D.; Udomsasporn, K.; Yotphan, S. *J. Org. Chem.* **2015**, *80*, 3447.

18. Quan, X.J.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. *Org. Lett.,* **2014**, *16*, 5728.

19. Kumar, S.; Dubey, S.; Saxena, N.; Awasthi, S. K. *Tetrahedron letters* **2014**, *55*, 6034.