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## Direct N-heterocyclization of hydrazines to access styrylated pyrazoles: synthesis of 1,3,5-trisubstituted pyrazoles and dihydropyrazoles†

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A microwave-assisted method has been developed for the synthesis of tri-substituted pyrazoles via direct N-heterocyclization of hydrazines with metal-acetylacetone and -dibenzylideneacetonate without using any base or additives. Most importantly, the synthesis of 1-aryl-5-phenyl-3-styryl-1*H*-pyrazoles was achieved in a single step using hydrochloride salt of various phenylhydrazines and this is the first report for direct construction of these molecules. The reaction medium and microwave conditions play a critical role for their selective product formation during the reaction. The present reaction explored the usage of metal-diketonic complexes as reaction substrates providing acetylacetone and dibenzylideneacetonate moieties to directly participate in cyclization with hydrazines to form the corresponding pyrazoles in excellent yields. The present protocol introduces the important N-heterocyclic moieties in the final structures, giving the reaction great applications from a medicinal chemistry perspective, particularly in the late stage modification strategies in drug discovery.

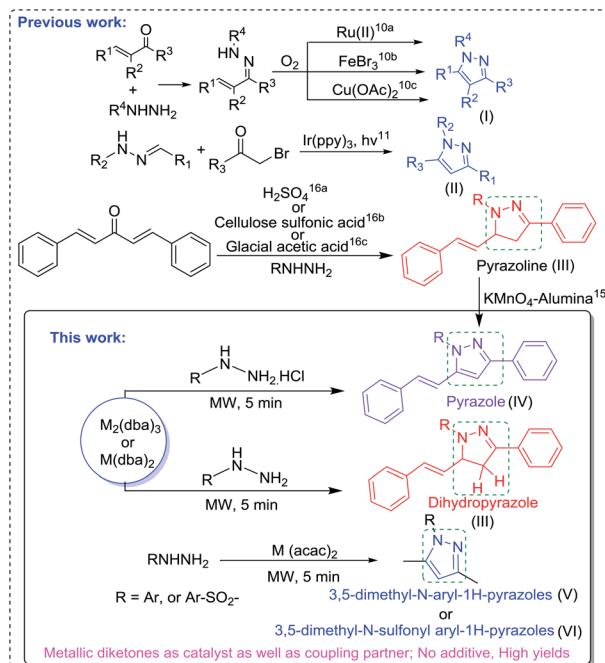
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## 1. Introduction

Pyrazoles are very important functional moieties having extensive applications in pharmaceuticals,<sup>1</sup> agriculture,<sup>2</sup> supramolecular chemistry,<sup>3</sup> polymers,<sup>4</sup> liquid crystals,<sup>5</sup> ligands in catalysis<sup>6</sup> and many others. Despite the intricacy in N–N bond formations, these are widely present in nature<sup>7</sup> such as in withasomine, pyrazofurin, formycin A and B, nostocine A, fluviol A–E, and pyrazole-3(5)-carboxylic acid and show remarkable biological potential. 1,3,5-Trisubstituted pyrazoles constitute a number of drugs,<sup>1,6,8</sup> including sildenafil (inhibits phosphodiesterase), celecoxib (selective COX-2 inhibitor used for inflammation and arthritis), rimonabant (inverse agonist for cannabinoid receptor CB1 and anti-obesity drug) and difenamizole (analgesic). In recent times, these are one of the privileged scaffolds in drug discovery and are extensively targeted by synthetic chemists. A number of methods have been developed to construct pyrazole scaffolds.<sup>9</sup> Traditionally, 1,3,5-trisubstituted pyrazoles are

synthesized by cyclocondensation of hydrazines with diketones under acidic conditions,<sup>10</sup> aromatization of pyrazolines<sup>11</sup> and intramolecular coupling of hydrazones.<sup>12</sup>



Scheme 1 Synthesis of pyrazoles and dihydropyrazoles.

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Recently, pyrazoles have been synthesized from imine hydrazine precursors (I, II) by cyclization using metal catalyst and oxidants or base<sup>13</sup> and from addition of hydrazones by  $\alpha$ -bromo ketones using light irradiation.<sup>14</sup>

Among 1,3,5-trisubstituted pyrazoles, the synthesis of 1-aryl-5-phenyl-3-styryl-1*H*-pyrazoles require pre-installed pyrazolines (III) as a substrate<sup>15</sup> for further oxidation to pyrazoles (Scheme 1). To date, we could not come across any report in our thorough literature search for the direct synthesis of 1-aryl-5-phenyl-3-styryl-1*H*-pyrazoles (IV) in one step. The electrocyclization of dibenzylideneacetones with hydrazines leads to the synthesis of pyrazolines (III) in the presence of a catalyst (Scheme 1).<sup>16</sup> Metal-acetylacetones [M(acac)<sub>2</sub>] and metal-dibenzylideneacetones [M<sub>2</sub>(dba)<sub>3</sub> or M(dba)<sub>2</sub>] are very powerful reagents in organic synthesis and catalysis. However, these metal complexes have not been used till date as a partner substrate for the construction of pyrazoles. As envisioned, herein, we disclose a general method for N-heterocyclization of different arylhydrazines with metal-diketonic complexes to access 1,3,5-trisubstituted pyrazoles, namely, 1-aryl-5-phenyl-3-styryl-1*H*-pyrazoles (IV), 3,5-dimethyl-*N*-aryl-1*H*-pyrazoles (V), 3,5-dimethyl-*N*-sulfonyl aryl-1*H*-pyrazoles (VI) and 1,3-diphenyl-5-styryl-4,5-dihydro-1*H*-pyrazole (III), under neutral conditions using microwave irradiations (Scheme 1).

## 2. Results and discussion

To investigate the optimized conditions for the synthesis of styryl substituted pyrazoles (A), we choose phenyl hydrazine hydrochloride as a model substrate. The reaction of model substrate with Pd<sub>2</sub>(dba)<sub>3</sub> was performed in different solvents under microwave irradiation at 100 °C and 50 watt for 5 min (Table 1). Reaction with phenylhydrazine hydrochloride in H<sub>2</sub>O gave both pyrazole as well as dihydropyrazole in approximately equal amounts (Table 1, entry 1). However, interestingly, in the case of phenyl hydrazine substrate (without hydrochloride salt), the reaction gave styryl-substituted dihydropyrazole (B) as the major product (Table 1, entry 9). DMSO afforded the desired styryl-substituted pyrazole in high yield (Table 1, entry 2). In case of DMF, the reaction did not give pyrazole (A) product, but only 10% of dihydropyrazole (B) was observed (Table 1, entry 3).

Reaction in CHCl<sub>3</sub> and toluene selectively provided the pyrazole (A) product. However, very less conversion was observed (Table 1, entries 6 and 8). Other solvents such as MeOH, PEG-200 and THF also did not provide promising yields and selectivity of the desired pyrazole (A) product (Table 1, entries 4, 5 and 7).

Thereafter, we investigated the scope for an important finding in the present report, *i.e.* direct synthesis of 1-aryl-5-phenyl-3-styryl-1*H*-pyrazoles from the reaction of phenyl hydrazine hydrochlorides (Table 2). The reaction of trifluoromethoxy, nitrile, methoxy and trifluoro methyl-substituted hydrazines afforded 1-aryl-5-phenyl-3-styryl-1*H*-pyrazoles in good yields (Table 2, 2a-2d) with Pd<sub>2</sub>(dba)<sub>3</sub> using DMSO as a solvent instead of H<sub>2</sub>O. Halogenated (Cl, F, Br) phenylhydrazines also gave the desired product in high yields (Table 2, 2e-2j). The reaction of phenylhydrazine hydrochloride proceeded well under optimised conditions (Table 2, 2k).

Table 1 Optimization of conditions for formation of styryl pyrazoles<sup>a</sup>

Entry	Solvent	MW (watts)	Yield <sup>b</sup> [%]	
			A	B
1	H <sub>2</sub> O	50	30	25
2	DMSO	50	80	5
3	DMF	50	0	10
4	MeOH	50	20	10
5	PEG-200	50	5	8
6	CHCl <sub>3</sub>	50	15	0
7	THF	50	20	6
8	Toluene	50	10	0
9 <sup>c</sup>	H <sub>2</sub> O	50	5	89

<sup>a</sup> Reaction conditions: phenyl hydrazine hydrochloride (1.0 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.5 equiv.), solvent (1 mL), MW (watts), 100 °C, for 5 min.

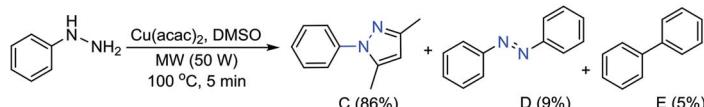
<sup>b</sup> Isolated yields. <sup>c</sup> Reaction with phenyl hydrazine (no HCl salt).

To obtain the dihydropyrazole product, reaction of Pd<sub>2</sub>(dba)<sub>3</sub> was carried out with various substituted phenylhydrazines in H<sub>2</sub>O. The reaction of trifluoromethoxy, nitrile and halides (F, Cl, Br) substituted phenyl hydrazines afforded the corresponding dihydropyrazoles in good yields (Table 2, 2l-2s). Also, phenylhydrazine gave the desired product in high yield (Table 2, 2t). Following this, we thought to explore the scope of the current

Table 2 Synthesis of pyrazoles and dihydropyrazoles<sup>abcd</sup>

	R = p-OCF <sub>3</sub>	R = p-CN	R = p-OCF <sub>3</sub>	R = p-CN
2a, 71%	2b, 70%	2c, 69%	2d, 76%	2e, 78%
R = p-OCH <sub>3</sub>	R = m-Cl	R = m-Br	R = p-Cl	R = p-Cl
2e, 69%	2f, 69%	2g, 73%	2i, 64%	2j, 67%
R = m-Br	R = p-F	R = p-Br	R = p-F	R = p-Br
2g, 73%	2h, 70%	2k, 74% (77%) <sup>e</sup>	2i, 64%	2k, 74% (77%) <sup>e</sup>
R = H, 2k, 74% (77%) <sup>e</sup>				
R' = p-F	R' = p-Cl	R' = p-Br	R' = p-Cl	R' = p-Br
2r, 80%	2s, 83%	2t, 89% (86%) <sup>e</sup>	2q, 85%	2t, 89% (86%) <sup>e</sup>
R' = p-Cl	R' = H	R' = H	R' = H	R' = H

<sup>a</sup> Reaction conditions: hydrazine (1.0 mmol), Pd(dba)<sub>3</sub> (0.5 equiv.), MW (50 watts), 100 °C, for 5 min. <sup>b</sup> Isolated yields. <sup>c</sup> DMSO (1 mL) was used as solvent for synthesis of pyrazoles (5a-5k). <sup>d</sup> H<sub>2</sub>O (1 mL) was used as solvent for synthesis of dihydropyrazoles (5l-5t). <sup>e</sup> Yields in parenthesis are with Pd(dba)<sub>2</sub> (0.5 equiv.).



Scheme 2 Formation of pyrazole and/or other products (azobenzene and biphenyl) using phenylhydrazine and M(acac)<sub>2</sub> in DMSO.

methodology for other metal complexes that could be used as coupling partners. Initially, the reaction of phenyl hydrazine with Cu(acac)<sub>2</sub> in DMSO was performed to optimize the conditions under microwave irradiation (Scheme 2).

To extend the scope of various substituted pyrazoles, we screened different solvents with the Cu(acac)<sub>2</sub> on model substrates (Table 3, entries 1–8) and among them, H<sub>2</sub>O (96%), DMSO (89%) and THF (90%) provided the desired 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**C**) in high yields. In case of DMF and toluene, azobenzene (**D**) was observed as the major (>90%) product (Table 3, entries 3 and 8). Undoubtedly, an ideal solvent H<sub>2</sub>O was selected for further study. Furthermore, the reaction with different metal (Cu, Co, Pd, Ni, Cr, Mn)-diketones were also explored; the results showed the formation of the desired pyrazole in good to excellent yields (63–96%). To our delight, Cu(acac)<sub>2</sub> showed the best results (Table 3, entries 1 and 9–13). The required minimum amount of Cu(acac)<sub>2</sub> for the reaction was also optimized (Table 3, entries 1 and 14–16). On decreasing the amount to 0.5 equiv., yield of the product was not affected (Table 3, entry 17). However, on further decreasing

the amount drastically, the yield of the product greatly reduced (Table 3, entries 14 and 15). The increase in microwave (MW) power did not influence the yields per time of the present reaction (Table 3, entries 17 and 18).

The present reaction was explored for the synthesis of various 1,3,5-trisubstituted pyrazoles. Different types of functional groups were tolerated under the present reaction conditions. The reaction of phenyl hydrazine gave the desired pyrazole in 96% yield (Table 4, **3a**). Halogen bearing phenyl hydrazines proceeded well and afforded the corresponding 1,3,5-trisubstituted pyrazoles in high yields (Table 4, **3b–3j**). Nitrile, nitro, methoxy, methyl and methylenedioxy accommodated phenyl hydrazines also gave the corresponding pyrazoles in excellent yields (Table 4, **3k–3p**). The labile ester group remained intact in the final product during the reaction (Table

Table 3 Optimization of conditions for 3,5-dimethyl substituted pyrazole<sup>a</sup>

Entry	M(acac) <sub>2</sub> (equiv.)	Solvent	MW (watts)	Yield <sup>b</sup> [%]
1	Cu(acac) <sub>2</sub> (1)	H <sub>2</sub> O	50	96
2	Cu(acac) <sub>2</sub> (1)	DMSO	50	86
3 <sup>c</sup>	Cu(acac) <sub>2</sub> (1)	DMF	50	0
4	Cu(acac) <sub>2</sub> (1)	MeOH	50	35
5	Cu(acac) <sub>2</sub> (1)	PEG-200	50	63
6	Cu(acac) <sub>2</sub> (1)	CHCl <sub>3</sub>	50	52
7	Cu(acac) <sub>2</sub> (1)	THF	50	90
8 <sup>d</sup>	Cu(acac) <sub>2</sub> (1)	Toluene	50	6
9	Co(acac) <sub>2</sub> (1)	H <sub>2</sub> O	50	89
10	Pd(acac) <sub>2</sub> (1)	H <sub>2</sub> O	50	88
11	Ni(acac) <sub>2</sub> (1)	H <sub>2</sub> O	50	72
12	Cr(acac) <sub>2</sub> (1)	H <sub>2</sub> O	50	65
13	Mn(acac) <sub>2</sub> (1)	H <sub>2</sub> O	50	63
14	Cu(acac) <sub>2</sub> (0.05)	H <sub>2</sub> O	50	9
15	Cu(acac) <sub>2</sub> (0.25)	H <sub>2</sub> O	50	45
16	Cu(acac) <sub>2</sub> (0.5)	H <sub>2</sub> O	50	96
17	Cu(acac) <sub>2</sub> (0.05)	H <sub>2</sub> O	100	95
18	Cu(acac) <sub>2</sub> (1)	H <sub>2</sub> O	100	96

<sup>a</sup> Reaction conditions: phenyl hydrazine (1.0 mmol), M(acac)<sub>2</sub> (equiv.), solvent (1 mL), MW (watts), 100 °C, for 5 min. <sup>b</sup> Isolated yields.

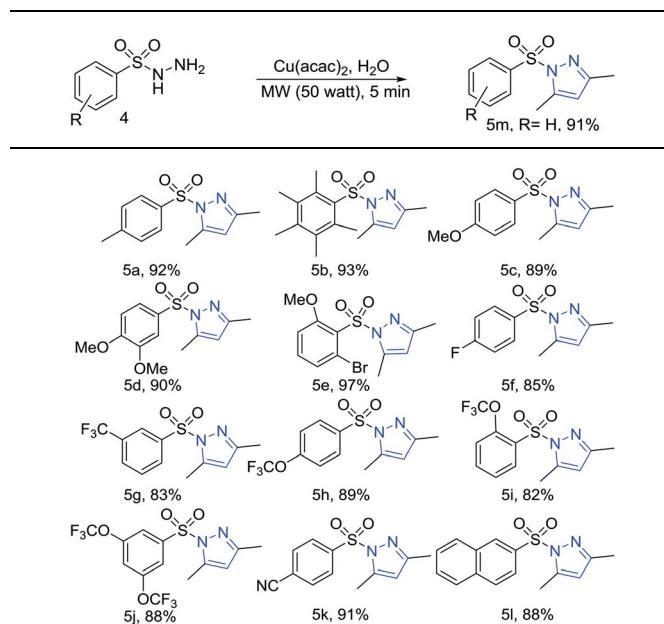
<sup>c</sup> Azobenzene (40%) and biphenyl (60%) were formed as major products. <sup>d</sup> Azobenzene was formed as major product (96%).

Table 4 Synthesis of 1,3,5-trisubstituted pyrazoles<sup>ab</sup>

1	Cu(acac) <sub>2</sub> , H <sub>2</sub> O MW (50 Watts), 5 min	3
	3a, 96%	
	3c, 86%	
	3d, 87%	
	3g, 95%	
	3i, 89%	
	3k, 91%	
	3m, 96%	
	3o, 92%	
	3q, 90%	

<sup>a</sup> Reaction conditions: hydrazine (1.0 mmol), Cu(acac)<sub>2</sub> (0.5 equiv.), H<sub>2</sub>O (1 mL), MW (50 watts), 100 °C, for 5 min. <sup>b</sup> Isolated yields.



Table 5 Synthesis of 3,5-dimethyl-N-sulfonyl aryl-1*H*-pyrazoles<sup>a,b</sup>

<sup>a</sup> Reaction conditions: sulfonylhydrazine (1.0 mmol), Cu(acac)<sub>2</sub> (0.5 equiv.), H<sub>2</sub>O (1 mL), MW (50 watts), 100 °C, for 5 min. <sup>b</sup> Isolated yields.

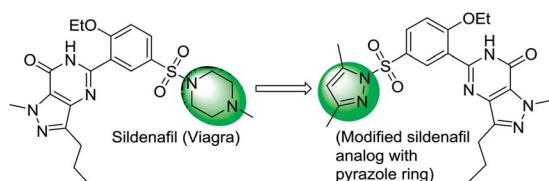


Fig. 1 Direct application of method in preparation of pyrazole analogue of sildenafil.

4, 3q). The reaction of hydrazine having the heterocyclic ring system, *i.e.*, 2-hydrazinopyridine, afforded the corresponding pyrazole product in high yield (Table 4, 3r).

Next, with the thought of further expanding the scope of the reaction, we moved our attention towards applying the methodology on sulfonyl hydrazines. The reaction with various substituted aryl sulfonylhydrazines such as methyl, methoxyl, halides, trifluoromethyl, trifluoromethoxy, nitrile, and naphthalene substituted sulfonyl hydrazines gave the corresponding arylsulfonyl pyrazoles in excellent yields (Table 5, 5a–5m).

As an extension of the present method, a typical example of alkyl-hydrazine, *i.e.*, phenethylhydrazine hydrochloride, was reacted under the optimized conditions, in which the desired product 3,5-dimethyl-1-phenethyl-1*H*-pyrazole (see ESI†) was obtained in trace amount.

The present protocol was applied in some complex molecules to elaborate the commercial importance in late stage modifications. In continuation to our ongoing project for the synthesis of selective PDE5 inhibitors,<sup>17</sup> the pyrazole-bearing analogue with different heterocyclic moiety in the native structure of sildenafil (Fig. 1) was prepared only to show the utility of method in late stage modifications of important drug scaffolds.

### 3. Conclusions

In conclusion, we have developed a new method for direct N-heterocyclization of hydrazines with metal-diketones for the synthesis of various trisubstituted pyrazoles under microwave irradiation offering excellent yields. The synthesis of 1-aryl-5-phenyl-3-styryl-1*H*-pyrazoles was achieved in a single step, which is the most important finding in the present method. In addition to the various substituted phenyl hydrazines, this method was also applicable to various sulfonyl hydrazines, which are very important functional moieties in drug discovery. To ascribe the late stage modification importance of the present methodology, pyrazole analogue of sildenafil was also prepared. Bringing N-heterocyclic moieties, pyrazoles, in the final structure in a single step, the present method could have great importance in medicinal chemistry or drug discovery.

### Conflicts of interest

There are no conflicts to declare.

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### Notes and references

- (a) C. E. Mowbray, C. Burt, R. Corbau, S. Gayton, M. Hawes, M. Perros, I. Tran, D. A. Price, F. J. Quinton, M. D. Selby, P. A. Stupple, R. Webster and A. Wood, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5857; (b) P. G. Wyatt, A. J. Woodhead, V. Berdini, J. Boulstridge, M. G. Carr, D. M. Cross, D. J. Davis, L. A. Devine, T. R. Early, R. E. Feltell, E. J. Lewis, R. L. MsMenamin, E. F. Navarro, M. A. O'Brien, M. O'Reilly, M. Reule, G. Saxty, L. A. Seavers, D. M. Smith, M. Squires, G. Trewartha, M. T. Walker and A. J. A. Woolford, *J. Med. Chem.*, 2008, **51**, 4986; (c) P. Wickens, H. Kluender, J. Dixon, C. Brennan, F. Achebe, A. Bacchicchi, D. Bankston, D. Bierer, M. Brands, D. Braun, M. S. Brown, C. Y. Chuang, J. Dumas, I. Enyedy, G. Hofliena, Z. Hong, T. Housley, B. Jones, U. Khire, C. Kreiman, E. Kumarasinghe, T. Lowinger, R. Ott-Morgan, L. Perkins, B. Phillips, R. Schoenleber, W. J. Scott, R. Sheeler, A. Redman, X. Sun, I. Taylor, L. Wang, S. Wilhelm, X. Zhang, M. Zhang, E. Sullivan, C. Carter, M. Miglarese and J. Levy, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4378; (d) T. de Paulis, K. Hemstapat, Y. Chen, Y. Zhang, S. Saleh, D. Alagille, R. M. Baldwin, G. D. Tamagnan and P. J. Conn, *J. Med. Chem.*, 2006, **49**, 3332; (e) A. A. Bekhit and T. Abdel-Aziem, *Bioorg. Med. Chem.*, 2004, **12**, 1935; (f) A. Tanitame, Y. Oyamada, K. Ofuji, M. Fujimoto, K. Suzuki, T. Ueda, H. Terauchi, M. Kawasaki, K. Nagai, M. Wachi



and J. I. Yamagishi, *Bioorg. Med. Chem.*, 2004, **12**, 5515; (g) K. M. Kasiotis, E. N. Tzanetou and S. A. Haroutounian, *Front. Chem.*, 2014, **2**, 78; (h) A. Balbi, M. Anzaldi, C. Maccio, C. Aiello, M. Mazzei, R. Gangemi, P. Castagnola, M. Miele, C. Rosano and M. Viale, *Eur. J. Med. Chem.*, 2011, **46**, 5293; (i) M. F. Khan, M. M. Alam, G. Verma, W. Akhtar, M. Akhter and M. Shaquiquzzaman, *Eur. J. Med. Chem.*, 2016, **120**, 170.

2 (a) F. Giornal, S. Pazenok, L. Rodefeld, N. Lui, J. P. Vors and F. R. Leroux, *J. Fluorine Chem.*, 2013, **152**, 2; (b) J. Jaunzem and M. Braun, *Org. Process Res. Dev.*, 2014, **18**, 1055; (c) P. Lei, X. Zhang, Y. Xu, G. Xu, X. Liu, X. Yang, X. Zhang and Y. Ling, *Chem. Cent. J.*, 2016, **10**, 40.

3 (a) M. A. Halcrow, *Dalton Trans.*, 2009, 2059; (b) J. Perez and L. Riera, *Eur. J. Inorg. Chem.*, 2009, **2009**, 4913; (c) I. R. Fernando, S. Jianrattanasawat, N. Daskalakis, K. D. Demadis and G. Mezei, *CrystEngComm*, 2012, **14**, 908; (d) M. Ishida, H. Fujimoto, T. Morimoto, S. Mori, M. Togano, S. Shimizu and H. Furuta, *Supramol. Chem.*, 2017, **29**, 8.

4 (a) V. Mukundam, A. Kumar, K. Dhanunjayara, A. Ravi, S. Peruncheralathan and K. Venkatasubbaiah, *Polym. Chem.*, 2015, **6**, 7764; (b) S. Carlotto, M. Casarin, A. Lanza, F. Nestola, L. Pandolfo, C. Pettinari and R. Scatena, *Cryst. Growth Des.*, 2015, **15**, 5910.

5 (a) M. Viciano-Chumillas, S. Tanase, L. Jos de Jongh and J. Reedijk, *Eur. J. Inorg. Chem.*, 2010, **2010**, 3403; (b) J. Olguin and S. Brooker, *Coord. Chem. Rev.*, 2011, **255**, 203.

6 (a) B. H. Pearce, H. F. Ogunu and R. C. Luckay, *Eur. J. Inorg. Chem.*, 2017, 1189; (b) F. Estevan, P. Hirva, A. Ofori, M. Sanau, T. Spec and M. Ubeda, *Inorg. Chem.*, 2016, **55**, 2101; (c) W. D. Bailey, L. Luconi, A. Rossin, D. Yakhvarov, S. E. Flowers, W. Kaminsky, R. A. Kemp, G. Giambastiani and K. I. Goldberg, *Organometallics*, 2015, **34**, 3998.

7 V. Kumar, K. Kaur, G. K. Gupta and A. K. Sharma, *Eur. J. Med. Chem.*, 2013, **69**, 735.

8 A. Ansari, A. Ali, M. Asif and Shamsuzzaman, *New J. Chem.*, 2017, **41**, 16.

9 (a) M. Suri, T. Jousseaume, J. J. Neumann and F. Glorius, *Green Chem.*, 2012, **14**, 2193; (b) P. Prasanna, S. Perumal and J. C. Menéndez, *Green Chem.*, 2013, **15**, 1292; (c) Q. Wang, Z. Zhang, Z. Du, H. Hua and S. Chen, *Green Chem.*, 2013, **15**, 1048; (d) F. Li, J. Nie, L. Sun, Y. Zheng and J. A. Ma, *Angew. Chem., Int. Ed.*, 2013, **52**, 6255; (e) R. Harigae, K. Moriyama and H. Togo, *J. Org. Chem.*, 2014, **79**, 2049; (f) S. Dadiboyena and A. Nefzi, *Eur. J. Med. Chem.*, 2011, **46**, 5258; (g) S. Fustero, M. Sánchez-Roselló, P. Barrio and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984; (h) J. L. Tang, L. Ming and X. M. Zhao, *J. Heterocyclic Chem.*, 2016, **53**, 1367–1370.

10 (a) L. Knorr, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 2587; (b) V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro and J. Elguero, *Eur. J. Org. Chem.*, 2004, **117**, 4348; (c) S. T. Heller and S. R. Natarajan, *Org. Lett.*, 2006, **8**, 2675; (d) E. Vickerstaffe, B. H. Warrington, M. Ladlow and S. V. J. Ley, *Comb. Chem.*, 2004, **6**, 332; (e) S. K. Singh, M. Srinivasa Reddy, S. Shivaramakrishna, D. Kavitha, R. Vasudev, J. M. Babu, A. Sivalakshmidevi and Y. Rao, *Tetrahedron Lett.*, 2004, **45**, 7679; (f) V. Polshettiwar and R. S. Varma, *Tetrahedron*, 2010, **66**, 1091; (g) A. DeAngelis, D. H. Wang and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 3434; (h) W. Jin, H. F. Yu and Z. K. Yu, *Tetrahedron Lett.*, 2011, **52**, 5884.

11 (a) M. Zolfigol, D. Azarifar and B. Maleki, *Tetrahedron Lett.*, 2004, **45**, 2181; (b) L. Chai, Y. Zhao, Q. Sheng and Z. Q. Liu, *Tetrahedron Lett.*, 2006, **47**, 9283; (c) G. Su, W. T. Wu, J. T. Wang and L. M. Wu, *Chin. Chem. Lett.*, 2008, **19**, 1013; (d) N. Nakamichi, Y. Kawashita and M. Hayashi, *Org. Lett.*, 2002, **4**, 3955; (e) Y. Kawashita and M. Hayashi, *Molecules*, 2009, **14**, 3073; (f) G. S. Ananthnag, A. Adhikari and M. S. Balakrishna, *Catal. Commun.*, 2014, **43**, 240.

12 (a) T. H. Zhang and W. L. Bao, *J. Org. Chem.*, 2013, **78**, 1317; (b) J. T. Hu, S. Chen, Y. H. Sun, J. Yang and Y. Rao, *Org. Lett.*, 2012, **14**, 5030; (c) X. W. Li, L. He, H. J. Chen, W. Q. Wu and H. F. Jiang, *J. Org. Chem.*, 2013, **78**, 3636; (d) G. W. Zhang, Y. Zhao and H. B. Ge, *Angew. Chem., Int. Ed.*, 2013, **52**, 2559; (e) M. Zora and A. Kivrak, *J. Org. Chem.*, 2011, **76**, 9379; (f) P. Liu, Y. M. Pan, Y. L. Xu and H. S. Wang, *Org. Biomol. Chem.*, 2012, **10**, 4696; (g) Z. L. Li, J. H. Liu, Z. W. Huang, Y. Yang, C. G. Xia and F. W. Li, *ACS Catal.*, 2013, **3**, 839; (h) P. Rai, M. Srivastava, J. Singh and J. Singh, *RSC Adv.*, 2014, **4**, 779.

13 (a) J. Hu, S. Chen, Y. Sun, J. Yang and R. Yu, *Org. Lett.*, 2012, **14**, 5030; (b) T. Zhang and W. Bao, *J. Org. Chem.*, 2013, **78**, 1317; (c) X. Li, H. Li, H. Chen, W. Wu and H. Jiang, *J. Org. Chem.*, 2013, **78**, 3636.

14 X. W. Fan, T. Lei, C. Zhou, Q. Y. Meng, B. Chen, C. H. Tung and L. Z. Wu, *J. Org. Chem.*, 2016, **81**, 7127.

15 S. Naik and V. Desai, *Green Sustainable Chem.*, 2013, **3**, 1.

16 (a) K. N. V. C. Lakshmi, M. Venkatesh, J. Hareesh, B. S. Raju and B. Anupama, *Pharma Chem.*, 2016, **8**, 122; (b) Z. Daneshfar and A. Rostami, *RSC Adv.*, 2015, **5**, 104695; (c) V. N. Pathak, R. Joshi, J. Sharma, N. Gupta and V. M. Rao, *Phosphorus, Sulfur Silicon*, 2009, **184**, 1854.

17 (a) S. D. Sawant, G. L. Reddy, M. I. Dar, M. Srinivas, G. Gupta, P. K. Sahu, P. Mahajan, A. Nargotra, S. Singh, S. C. Sharma, M. Tikoo, G. Singh, R. A. Vishwakarma and S. H. Syed, *Bioorg. Med. Chem.*, 2015, **23**, 2121; (b) S. D. Sawant, G. L. Reddy, M. Srinivas, S. S. Hussain, M. I. Dar, A. Nargotra, P. Mahajan and R. A. Vishwakarma, WO 2015/114647 A1, 2015.

