

# Polysubstituted pyrrole derivatives via 1,2-alkenyl migration of novel $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehydes and $\alpha$ -diazocarbonyls†

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Tri-substituted pyrrole derivatives were successfully synthesized from aminoaldehyde and  $\alpha$ -diazocarbonyl, using a  $\text{TiCl}_4$  catalyst. The reactions proceeded via 1,2-migration and condensation, leading to the corresponding pyrroles in moderate to excellent yields. Reaction susceptibility was subsequently demonstrated by the variation in substrates.

In the field of pyrrole synthesis, the continuous efforts to develop competent strategies emphasize the inadequacy of the currently available methods. Probing into the existing methods provided an insight to the inefficacy as well as substantiated the need to refine and surpass current approaches. The use of non-environmental catalysts,<sup>1</sup> harsh reaction conditions and deprived yields<sup>2</sup> contributed to the general consensus that there is still a huge underlying potential in pyrrole synthesis. Not only are pyrroles omnipresent in natural products<sup>3,4</sup> and drugs<sup>5,6</sup> (Fig. 1), they also exhibit a wide range of biological activities (anti-inflammatory,<sup>7</sup> antibiotic<sup>8</sup> and anti-tumour<sup>9</sup> activities), provide an excellent choice in catalytic systems<sup>10</sup> and adopt a leading spot over other aromatic heterocycles in drug discovery.<sup>11</sup> With such compelling benefits, it is not surprising that their synthesis has engaged the chemical society over the past century.

Classical approaches to the synthesis of substituted pyrroles often revolve around the concept of Paal–Knorr synthesis in 1884.<sup>12,13</sup> This work, involving the reaction between an amine and a 1,4-dicarbonyl compound, has brought great expansion to the otherwise limited synthesis of pyrroles. Noteworthy, other conventional methods such as Huisgen<sup>12</sup> and Hantzsch<sup>13</sup> pyrrole synthesis have also contributed significantly to the development of pyrrole derivatives. Over the past decades,

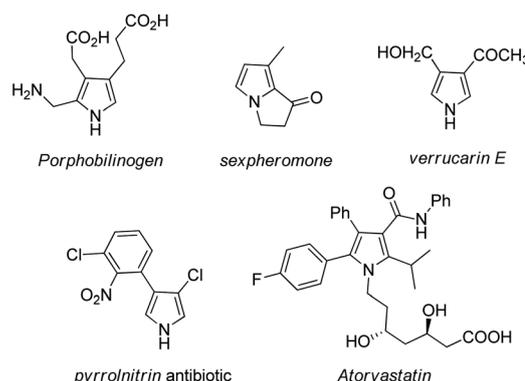


Fig. 1 Pyrrole-containing natural products/drugs.

various strategies which attempted to improve on these traditional approaches have emerged and produced remarkable results, such as multi-component one-pot reactions<sup>14</sup> and palladium catalyzed C–H activation.<sup>15</sup> They served as alternatives to synthesize poly-functionalized pyrrole derivatives and have created excellent opportunities for researchers. Inspired by the abundant benefits and possibilities, our group has decided to develop new methodologies in the synthesis of pyrrole derivatives,<sup>16</sup> continuing our constant efforts in the construction of heterocyclic compounds.<sup>17–20</sup> Successful representations of transition metal-catalyzed 1,2-migration in the assembly of heterocycles<sup>21,22</sup> sparked off our interests in adopting this method for the synthesis of pyrroles. A widely used and highly efficient strategy in organic synthesis, 1,2-migration can be generally classified into 1,2-hydride,<sup>23</sup> alkyl,<sup>24</sup> aryl and alkenyl migration.<sup>25,26</sup> Although the reactions involving 1,2 migrations generally produce promising results, 1,2-alkenyl migration seems to be less prevalent in contrast to the other categories. Therefore, due to the increasing popularity of diazo compounds at the same time, we envisioned the possibility of using diazo compounds to participate in a 1,2-alkenyl migration, forming pyrrole derivatives simultaneously.<sup>27,28</sup> The generation of metal carbene species through the diazo compounds provides diverse

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reactivities, which in turn helps to induce 1,2-shift formations, cyclopropanations and bond insertions.<sup>29,30</sup> With the integration of both aspects, herein, we report an efficient synthesis of polysubstituted pyrrole derivatives through the addition of diazocarbonyl compounds to various  $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehydes. We envisioned that the successful execution of such a system will provide an interesting insight through the implementation of 1,2-alkenyl shift from novel  $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehydes (Table 1).

Preliminary studies focus on the optimization of a suitable and efficient set of conditions for the reaction between ethyl diazoacetate **2a** and *N*-Boc- $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde **1a**. The search began with the identification of an appropriate catalyst to encourage this reaction. Based on earlier reports, it could be observed that successful 1,2-migration often involves the incorporation of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  as the Lewis acid catalyst.<sup>25,31</sup> With this noticeable trend,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  naturally became the first choice of catalyst for the initial optimization. Although  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  appears to be a promising catalyst at the outset, no desired product was obtained when it was employed in this reaction. Therefore, the change in focus towards other possible catalyst was essential and further review of past literatures revealed  $\text{Rh}_2(\text{OAc})_4$  (ref. 32) and  $\text{SnCl}_4$  (ref. 33) as highly efficient catalysts for 1,2-shifts. While  $\text{Rh}_2(\text{OAc})_4$  did not manage to induce the reaction,  $\text{SnCl}_4$  successfully produced the desired product, albeit a relatively low yield (35%) was obtained with long reaction time. Despite the success of  $\text{SnCl}_4$  in obtaining the desired product, the search for an optimal catalyst continued as attempts to raise the yields through changing the solvent, reaction times and temperature were unproductive. After

several unsuccessful tries involving  $\text{ZnBr}_2$ ,  $\text{ZnCl}_2$  and  $\text{AlCl}_3$ ,  $\text{TiCl}_4$  was finally located as an efficient catalyst which could catalyze the reaction with a reasonably good yield of 63%.<sup>34</sup>

Having identified the suitable catalyst, other factors such as solvent and temperature were then taken into consideration and varied. When the reaction was subjected to reflux condition instead of normal room temperature, the yield was exponentially increased to 78%. In addition, after some analysis, it was found that  $\text{CH}_2\text{Cl}_2$  remains the most appropriate solvent in contrast to other common solvents such as toluene, DMF, MeCN and THF. Finally, the catalyst loading was modified and 10 mol% of the catalyst proves to be the best loading (similar results were produced at 20 mol% and less yield was obtained when the catalyst loading was decreased to 5 mol%). Consolidating the above mentioned experiment results; the optimal condition was elucidated as 10 mol% of  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$  at reflux temperature.

Acquirement of the ideal condition permitted investigation of the reaction's versatility through modification of the protecting group on  $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde **1** (Scheme 1). Although several protecting groups were screened, only the *tert*-butyloxycarbonyl (Boc) and the benzyl protecting groups were suitable for the reaction, obtaining yields of 78% and 55% respectively. Since the Boc protecting group proved superior over others, we carried out the screening of the substrates using *N*-Boc- $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde **1a**.

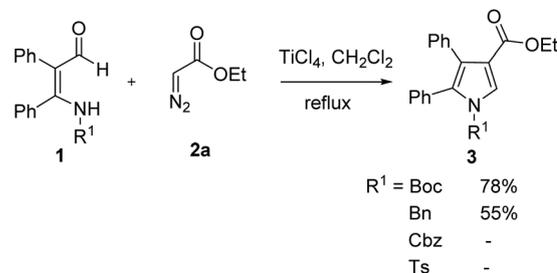
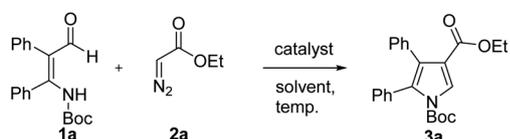
As the initial results amplified the suitability of diphenyl aldehydes, a range of electron donating and electron withdrawing substituents on the phenyl group was introduced (Scheme 2). Beginning from symmetrical diarylaminoaldehydes, the electron donating methyl-substituted **1b** was able to produce the pyrrole derivative **3b** in outstanding yield of 85%. Subjecting the reaction to electron withdrawing fluoro-substituted **3c** proved to be successful as well, obtaining a yield comparable to electron donating substituents (83%). To ensure that the reaction works on non-symmetrical diarylaminoaldehydes, single substituted methyl- and methoxy-**1d** and **1e** were synthesized and excellent yields were obtained for both compounds **3d** (83%) and **3e** (85%). However, when attempts to increase the scope were made by employing aliphatic aminoaldehyde, the reaction did not proceed as desired and no product was obtained.

Table 1 Optimization of the synthesis<sup>a</sup>

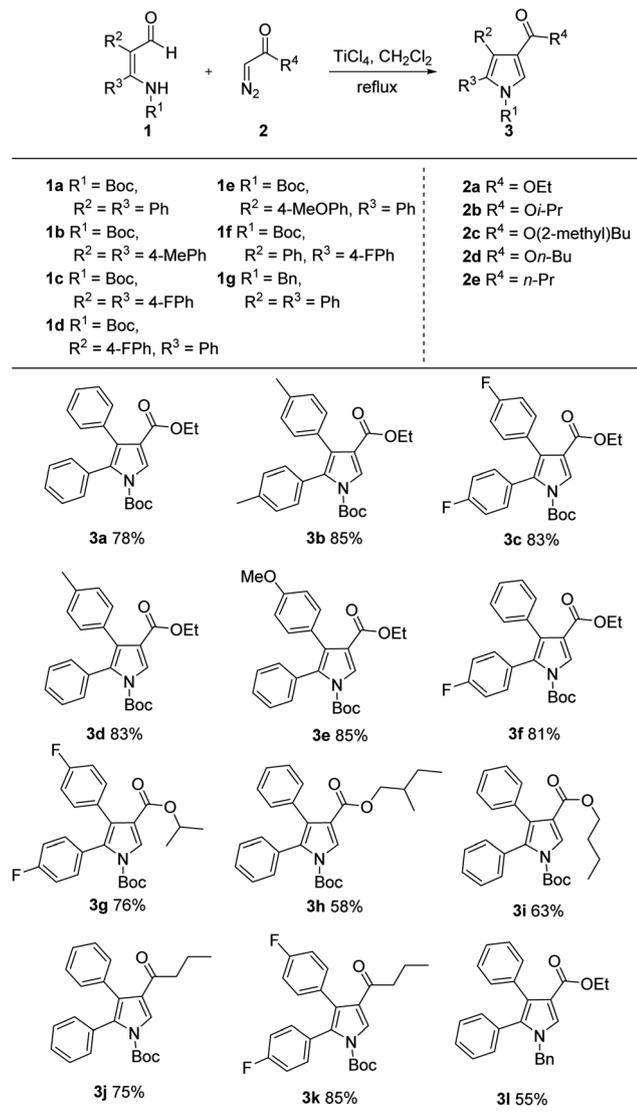
Entry	Catalyst	Solvent	Temp (°C)	Yield <sup>b</sup> (%)
1	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	$\text{CH}_2\text{Cl}_2$	r.t	—
2	$\text{Rh}_2(\text{OAc})_4$	$\text{CH}_2\text{Cl}_2$	r.t	n.r
3	$\text{SnCl}_4$	$\text{CH}_2\text{Cl}_2$	r.t	35
4	$\text{ZnBr}_2$	$\text{CH}_2\text{Cl}_2$	r.t	n.r
5	$\text{ZnCl}_2$	$\text{CH}_2\text{Cl}_2$	r.t	n.r
6	$\text{AlCl}_3$	$\text{CH}_2\text{Cl}_2$	r.t	n.r
7	$\text{TiCl}_4$	$\text{CH}_2\text{Cl}_2$	r.t	63
8	$\text{TiCl}_4$	$\text{CH}_2\text{Cl}_2$	Reflux	78
9	$\text{TiCl}_4$	Toluene	60	55
10	$\text{TiCl}_4$	THF	Reflux	28
11	$\text{TiCl}_4$	MeCN	r.t	20
12	$\text{TiCl}_4$	DMF	Reflux	—
13 <sup>c</sup>	$\text{TiCl}_4$	$\text{CH}_2\text{Cl}_2$	Reflux	64
14 <sup>d</sup>	$\text{TiCl}_4$	$\text{CH}_2\text{Cl}_2$	Reflux	79

<sup>a</sup> All reactions were conducted in  $\text{CH}_2\text{Cl}_2$  with 2.0 equiv. of aldehyde **1a** and 1.0 equiv. of  $\alpha$ -diazocarbonyl **2a** in the presence of 10 mol%  $\text{TiCl}_4$ .

<sup>b</sup> Isolated yield. <sup>c</sup> Reaction was conducted with 5 mol%  $\text{TiCl}_4$ . <sup>d</sup> Reaction was conducted with 20 mol%  $\text{TiCl}_4$ .

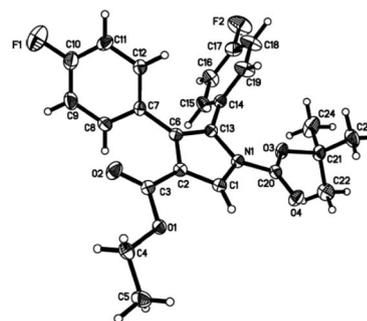


Scheme 1 Investigation of the amine protecting group in the synthesis of polysubstituted pyrrole derivatives. All reactions were conducted in  $\text{CH}_2\text{Cl}_2$  with 2.0 equiv. of *N*-protected- $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde **1** and 1.0 equiv. of  $\alpha$ -diazocarbonyl **2a** in the presence of 10 mol%  $\text{TiCl}_4$ . Isolated yield after chromatography.



**Scheme 2** Pyrrole derivatives from 1,2-migration of *N*-protected- $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde **1** and  $\alpha$ -diazocarbonyl **2**. Reactions were conducted in CH<sub>2</sub>Cl<sub>2</sub> with 1.0 equiv. of *N*-protected- $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde **1** and 2.0 equiv. of  $\alpha$ -diazocarbonyl **2** in the presence of 10 mol% TiCl<sub>4</sub>. Isolated yield.

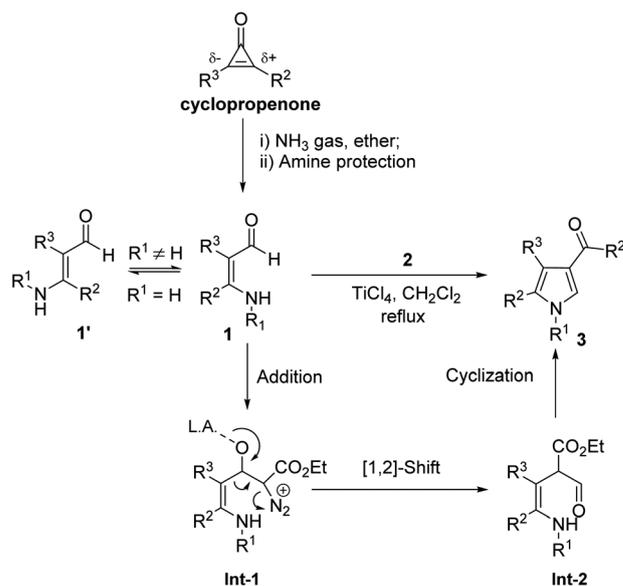
Having investigated the aminoaldehydes component, the investigation was then drawn towards modifying the  $\alpha$ -diazocarbonyls. Fixing on diazocarbonyl ester, branched ester substituents such as isopropyl ester **3g** and 2-methylbutyl ester **3h** were examined and the reactions were able to give good to moderate yields of 76% and 58% respectively. Finally, the successful application of diazopentan-2-one on both  $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde **3j** and difluoro-**3k** further indicated the tolerance of the reaction to an array of  $\alpha$ -diazocarbonyls. To round up on our investigation of the substrate scope, the protecting group of the  $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde was changed to benzyl group. Although the reaction was generally less satisfactory and slower as compared to using **Boc** protecting group, the pyrrole derivative **3l** was still obtained in a moderate yield of 55%.



**Fig. 2** X-ray structure of compound **3c**.

The crystal structure of the  $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde (ESI<sup>†</sup>) confirms with our theory that during the synthesis of this aldehyde, the ring opening of the non-symmetrical cyclopropanone occurs in a manner whereby the amine will attack the more electron deficient carbon site. This preference is largely influenced by the substituents on the phenyl ring (electron donating or withdrawing). Although the crystal structure shows a *trans*-form of the  $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde (**1f** without protecting group), it can be expected that such compounds are present in an equilibrium mixture of *trans*- and *cis*-isomers.<sup>35,36</sup> However, it is worthy of note that the *cis*-isomer might predominate after protection due to stabilization through intramolecular hydrogen bonding and steric hindrance.<sup>37</sup> Subsequently, confirmation of the structure of the polysubstituted pyrrole product was further done by obtaining the X-ray crystallography data of **3c** (Fig. 2).

With this product confirmation, a plausible mechanism can be deduced. Through a Lewis acid-catalyzed addition of diazoacetates with *N*-protected- $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehyde **1**, an alkoxide intermediate **Int-1** could be formed. A 1,2-alkenyl shift would then produce **Int-2**. Following which, cyclization would then result in the desired pyrroles **3** (Scheme 3).



**Scheme 3** Plausible synthetic pathway of 2,3-diaryl pyrroles.

In conclusion, successful reactions between  $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehydes and  $\alpha$ -diazocarbonyls were established. Polysubstituted pyrrole derivatives were obtained, using  $\text{TiCl}_4$  as the catalyst, in moderate to excellent yields. The flexibility of the reaction was demonstrated by the range of substrates, as well as protecting group. The successful implementation of this methodology provides profound potentials as pyrrole derivatives are essential components of many natural products and biological drugs. In addition, the similarity in structure to the natural product amforstatin indicates the possibility of using this straightforward strategy to the synthesis of this highly effective and largely in demand drug. Not only does this elegant methodology originate from the use of novel  $\gamma$ -amino- $\alpha,\beta$ -unsaturated aldehydes, the 1,2-alkenyl migration to produce polysubstituted pyrroles contributes an interesting discovery. Further studies for the application as well as extending the derivatives are underway.

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## References

- 1 T. V. Magdesieva, O. M. Nikitin, O. A. Levitsky, V. A. Zinovyeva, I. Bezverkhyy, E. V. Zolotukhina and M. A. Vorotyntsev, *J. Mol. Catal. A: Chem.*, 2012, **353**–354, 50–57.
- 2 Z. Zhang, J. Zhang, J. Tan and Z. Wang, *J. Org. Chem.*, 2008, **73**, 5180–5182.
- 3 M. G. Banwell, D. A. S. Beck, P. C. Stanislawski, M. O. Sydnes and R. M. Taylor, *Curr. Org. Chem.*, 2005, **9**, 1589–1600.
- 4 H. Hoffmann and T. Lindel, *Synthesis*, 2003, **2003**, 1753–1783.
- 5 M. Biava, G. C. Porretta, G. Poce, A. De Logu, R. Meleddu, E. De Rossi, F. Manetti and M. Botta, *Eur. J. Med. Chem.*, 2009, **44**, 4734–4738.
- 6 P. Rajender Kumar, S. Raju, P. SatishGoud, M. Sailaja, M. R. Sarma, G. Om Reddy, M. Prem Kumar, V. V. R. M. K. Reddy, T. Suresh and P. Hegde, *Bioorg. Med. Chem.*, 2004, **12**, 1221–1230.
- 7 I. K. Khanna, R. M. Weier, Y. Yu, P. W. Collins, J. M. Miyashiro, C. M. Koboldt, A. W. Veenhuizen, J. L. Currie, K. Seibert and P. C. Isakson, *J. Med. Chem.*, 1997, **40**, 1619–1633.
- 8 B. V. McInerney, R. P. Gregson, M. J. Lacey, R. J. Akhurst, G. R. Lyons, S. H. Rhodes, D. R. J. Smith, L. M. Engelhardt and A. H. White, *J. Nat. Prod.*, 1991, **54**, 774–784.
- 9 K. S. Kim, S. Lu, L. A. Cornelius, L. J. Lombardo, R. M. Borzilleri, G. M. Schroeder, C. Sheng, G. Rovnyak, D. Crews, R. J. Schmidt, D. K. Williams, R. S. Bhide, S. C. Traeger, P. A. McDonnell, L. Mueller, S. Sheriff, J. A. Newitt, A. T. Pudzianowski, Z. Yang, R. Wild, F. Y. Lee, R. Batorsky, J. S. Ryder, M. Ortega-Nanos, H. Shen, M. Gottardis and D. L. Roussell, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3937–3942.
- 10 R. A. Altman, K. W. Anderson and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 5167–5169.
- 11 J. W. Huffman and L. W. Padgett, *Curr. Med. Chem.*, 2005, **12**, 1395–1411.
- 12 R. Huisgen, H. Gotthardt, H. O. Bayer and F. C. Schaefer, *Angew. Chem., Int. Ed.*, 1964, **3**, 136–137.
- 13 A. Hantzsch, *Berichte der Deutschen Chemischen Gesellschaft*, 1890, **23**, 1474–1476.
- 14 V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Soc. Rev.*, 2010, **39**, 4402–4421.
- 15 E. Beck and M. Gaunt, *C-H Activation*, ed. J.-Q. Yu and Z. Shi, Springer, Berlin/Heidelberg, 2010, pp. 85–121
- 16 J. Zeng, Y. Bai, S. Cai, J. Ma and X.-W. Liu, *Chem. Commun.*, 2011, **47**, 12855–12857.
- 17 X. M. Cheng and X.-W. Liu, *J. Comb. Chem.*, 2007, **9**, 906–908.
- 18 S. Cai, J. Zeng, Y. Bai and X.-W. Liu, *J. Org. Chem.*, 2011, **77**, 801–807.
- 19 K. K. Pasunooti, H. Chai, C. N. Jensen, B. K. Gorityala, S. Wang and X.-W. Liu, *Tetrahedron Lett.*, 2011, **52**, 80–84.
- 20 Y. Bai, J. Zeng, J. Ma, B. K. Gorityala and X.-W. Liu, *J. Comb. Chem.*, 2010, **12**, 696–699.
- 21 Y. Xia, A. S. Dudnik, Y. Li and V. Gevorgyan, *Org. Lett.*, 2010, **12**, 5538–5541.
- 22 A. S. Dudnik, A. W. Sromek, M. Rubina, J. T. Kim, A. V. Kel'i and V. Gevorgyan, *J. Am. Chem. Soc.*, 2008, **130**, 1440–1452.
- 23 T. J. Donohoe, O. Williams and G. H. Churchill, *Angew. Chem., Int. Ed.*, 2008, **47**, 2869–2871.
- 24 F. Pfengle, A. Al-Harrasi, I. Brüdgam and H.-U. Reißig, *Eur. J. Org. Chem.*, 2009, **2009**, 282–291.
- 25 P. Levesque and P.-A. Fournier, *J. Org. Chem.*, 2010, **75**, 7033–7036.
- 26 T. Pei, C.-y. Chen, P. G. Dormer and I. W. Davies, *Angew. Chem., Int. Ed.*, 2008, **47**, 4231–4233.
- 27 Y. Zhang and J. Wang, *Chem. Commun.*, 2009, 5350–5361.
- 28 G. S. Singh and L. K. Mdee, *Curr. Org. Chem.*, 2003, **7**, 1821–1839.
- 29 D. M. Hodgson, F. Y. T. M. Pierard and P. A. Stuppel, *Chem. Soc. Rev.*, 2001, **30**, 50–61.
- 30 T. Ye and M. A. McKerverey, *Chem. Rev.*, 1994, **94**, 1091–1160.
- 31 J. M. Coxon, A. J. Thorpe and W. B. Smith, *J. Org. Chem.*, 1999, **64**, 9575–9586.
- 32 A. Goti, S. Cicchi, F. Cordero, V. Fedi and A. Brandi, *Molecules*, 1998, **4**, 1–12.
- 33 M.-T. Hsieh, H.-H. Chou, H.-J. Liu, H.-M. Wu, T. W. Ly, Y.-K. Wu and K.-S. Shia, *Org. Lett.*, 2009, **11**, 1673–1675.
- 34 M. E. Dudley, M. M. Morshed, C. L. Brennan, M. S. Islam, M. S. Ahmad, M.-R. Atuu, B. Branstetter and M. M. Hossain, *J. Org. Chem.*, 2004, **69**, 7599–7608.
- 35 (a) J. Dabrowski and L. Kozerski, *Chem. Commun.*, 1968, 586–587; (b) R. Parry, *Chem. Commun.*, 1967, 1294–1296.
- 36 J. Dabrowski and K. Kamienska-Trela, *Spectrochim. Acta*, 1966, **22**, 211–220.
- 37 T. Fumio, M. Tamio and A. Katushiko, *Chem. Commun.*, 1969, 229.