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Communication

Metal-free DBU promoted regioselective synthesis of isoxazoles and isoxazolines†‡

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A new simple and efficient metal-free 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) promoted regioselective synthesis of 3,5-disubstituted isoxazoles and isoxazolines from aldoximes has been described. This method allows reaction to proceed efficiently on aldoximes containing unprotected phenolic hydroxyl group. Furthermore, with the use of higher equivalents of N-chlorosuccinimide, chloro-substituted isoxazoles and isoxazolines were obtained as the only products via tandem one-pot 1,3-dipolar cycloaddition followed by regioselective chlorination.

Isoxazoles and isoxazolines are five-membered nitrogen containing heterocycles commonly found in variety of natural products and drugs and are known to exhibit wide range of pharmacological activities. The structures of biologically active isoxazoles/ isoxazolines **A-E** are shown in Figure 1.[1]

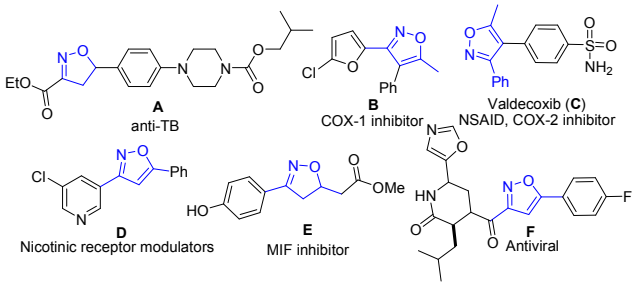

Figure 1. Examples of bioactive isoxazoles and isoxazolines

Although numerous methods have been reported for synthesis of isoxazoles,[2] the cycloaddition of alkynes with nitrile oxides is probably the most direct route to access these heterocycles. Uncatalyzed thermal cycloaddition reaction of nitrile oxide with alkyne is neither chemo- nor regioselective and, as a consequence, leads to formation of multiple products. Mostly the regioselectivity in this reaction has been achieved using Cu catalysts.[3] There also exists few metal-free protocols for synthesis of isoxazoles; however most of these reports involve use of hypervalent iodine.[2g, 4] Many hypervalent iodine reagents are explosive and have chemical reactivity issues.[5] Apart from the use of hypervalent iodine, only two other metal-free conditions (Et_3N,[6] $NaOCl/Et_3N$[7]) have been reported. However, the former reaction was not suitable for phenolic hydroxyl comtaining aldoximes; and later condition has been reported for only one example. The detailed substrate scope has never been established. In this context, we thought of exploiting this reaction to establish an efficient and elegant metal-free protocol for synthesis of isoxaxoles and isoxazolines with broad substrate scope. Our efforts identified 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as an excellent reagent which promotes 1,3-dipolar addition of nitrile oxides with alkynes/ alkenes without need of any metal catalyst. DBU has been reported to promote synthesis of variety of heterocyclic scaffolds such as isoquinolinones[8] and and benzothiazoles.[9] Herein, we report DBU-promoted synthesis of 3,5-disubstituted isoxazoles. Furthermore, we also report an interesting DBU-promoted tandem one-pot 1,3-dipolar cycloaddition reaction followed by regioselective chlorination (Figure 2).

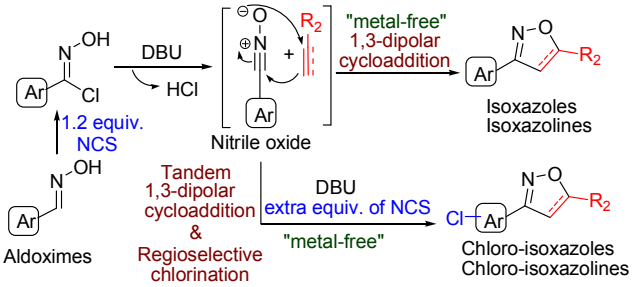

Figure 2. DBU promoted synthesis of isoxazoles and isoxazolines

Our investigations were started with the reaction of chloro-aldoxime **2a** with phenylacetylene **3a** in presence of 1 equiv DBU in chloroform, which produced desired 3,5-disubstituted isoxazole **4a** in 10 min in 95% yield (Figure 3). Next, we elaborated this method for direct synthesis of isoxazole **4a** from aldoxime **1a**. Under similar reaction conditions, when the reaction of 4-hydroxyphenyl aldoxime **2a** with phenylacetylene **3a** in presence of 1.2 equiv NCS was performed, multiple products were formed. Further, optimization studies indicated that DMF[10] is the best solvent for this reaction and sequential addition is required to get desired product in good yield (Figure 3). The sequential addition (**1a**+ NCS+DMF, rt, 1 h followed by addition of DBU and **3a**, rt, 10 min) was followed, to get product **4a** in good yield, without formation of side-products. However, when we performed this reaction (from **1a**) in presence of Et_3N (in place of DBU) under similar reaction conditions, multiple

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products were formed; which clearly indicated the superiority of our protocol over earlier Et_3N[6] method. The addition of DBU is slightly exothermic and quickly converts aldoximes to nitrile oxides which subsequently reacts with respective alkynes/alkenes to produce desired heterocycles. It is noteworthy to mention that the direct synthesis of hydroxy-substituted phenyl isoxazole **4a** from corresponding nitrile oxide has never been reported. The limitation of earlier methods for hydroxy-substituted phenyl nitrle oxides has also been mentioned.[3a] However, the present DBU-promoted synthesis provided this product in excellent yield.

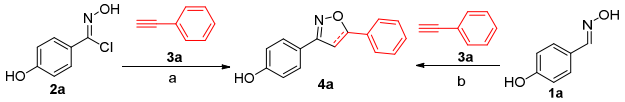

Figure 3. DBU-promoted synthesis of 4-hydroxy substituted isozaxole **4a**. Reagents and conditions: (a) 1 equiv DBU, $CHCl_3$, rt, 10 min, 95%; (b) 1 equiv DBU, 1.2 equiv NCS, DMF, 1 h, 80%.

Next, the substrate scope of the reaction was investigated for variety of aldoximes and phenylacetylenes (Figure 4). The optimized reaction condition involving the use of 1 equiv of DBU and 1.2 equiv of NCS was employed. Phenyl aldoxime along with those substituted with alkyl electron-donating groups produced isoxazoles in excellent yields (examples **4b**, **4d**, **4e**, and **4i**). In case of aldoximes substituted with other electron-donating groups such as OH, OMe (examples **4a**, **4c**, **4f**, **4g** and **4j**), desired products were formed in 65-80% yield. Interestingly, in latter reactions, additionally a ring-chlorinated isoxazole products were obtained as side products in 10-20% yield. Heterocyclic aldoximes also participated well in this reaction, producing desired products **4k** and **4l** in good yields. It is noteworthy to mention that the pyridine linked isoxazole **4l** prepared herein, has a close structural similarity to that of nicotine receptor modulator (structure **D**, Figure 1). Aliphatic oximes (example **4m**) and phenyl aldoxime with electron-withdrawing group (example **4n**) does not participated in this reaction. Among alkynes, all substituted phenylacetylenes participated well in this reaction, whereas aliphatic alkynes such as propargyl alcohol (example **4j**) and N-propargylated isatin (example **4h**) produced lower yields.

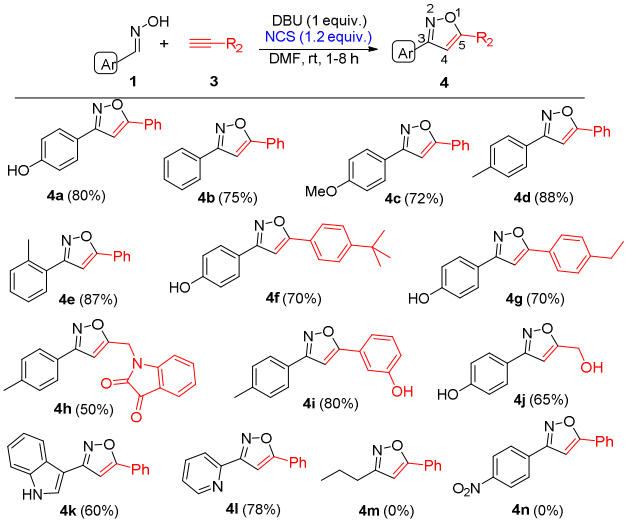

Figure 4. Scope of the reaction for synthesis of isoxazoles. Reagents and conditions: aldoxime (1 equiv.), alkyne (1.2 equiv.), DBU (1 equiv.), NCS (1.2 equiv.), DMF, 1-8 h, 50-88%. Reaction time:1 h for 4a, 4f, 4g and 4j; and 8 h for other examples.

Further, we examined the scope of this reaction for synthesis of various substituted isoxazolines using similar reaction conditions (Figure 5). Phenyl, *p*-tolyl and *m*-tolyl aldoximes gave good yields, irrespective of the location of alkyl substituent (examples **6f, 6g, 6i, 6k, 6l, 6n** and **6p**). Similarly, the electron-rich styrenes (examples **6h, 6i** and **6p**) and halo-substituted styrenes gave good yields. Among heteroaryl aldoximes, the pyridine aldoxime produced corresponding isoxazoline **6m** in good yield, whereas indole aldoxime produced corresponding isoxazoline **6q**, comparatively in a lesser yield.

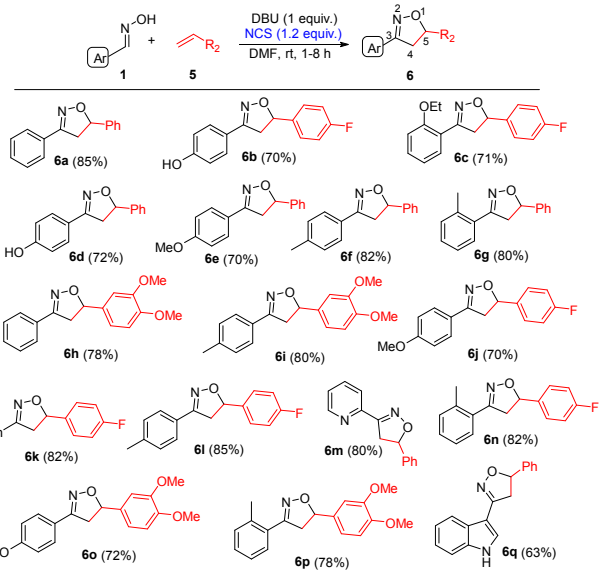

Figure 5. Scope of the reaction for synthesis of isoxazolines. Reagents and conditions: aldoxime (1 equiv.), styrene (1.2 equiv.), DBU (1 equiv.), NCS (1.2 equiv.), DMF, 1-8 h, 63-85%. Reaction time:1 h for **6b** and **6d**; and 8 h for other examples.

Next, we sought to explore the observed finding of one-pot 1,3-dipolar cycloaddition reaction followed by ring chlorination to produce chlorinated isoxazoles and isozaxolines (Figure 6). For this, we thought to use higher equivalents of NCS than the required amount, to get increased yields of chlorinated products. To our surmise, when aldoxime **1a** was treated with phenylacetylene **3a** in presence of 2.2 equivalents of NCS and 1 equiv of DBU, exclusively the chloro-substituted product **7a** was obtained (88% yield). Similarly, we prepared other chlorinated isoxazoles **7b**, **7c**, **7f** and **7g** using higher equivalents of NCS. The tandem one-pot 1,3-dipolar cycloaddition followed by regioselective chlorination also worked well for synthesis of chlorinated isoxazolines (Figure 6; examples **7d**, **7e** and **7h**). In case of furan-2-aldoxime, the isoxazole product **7g** was formed in good yield (90%), however lower yield (60%) was obtained for isoxazoline product **7h**. In case of indole-3-aldoxime and pyridine-2-aldoxime, ring chlorination product was not formed even after using higher equivalents of NCS. It is noteworthy to mention that the furyl compound **7g** has a structural similarity with reported COX-1 inhibitor (structure B, Figure 1).

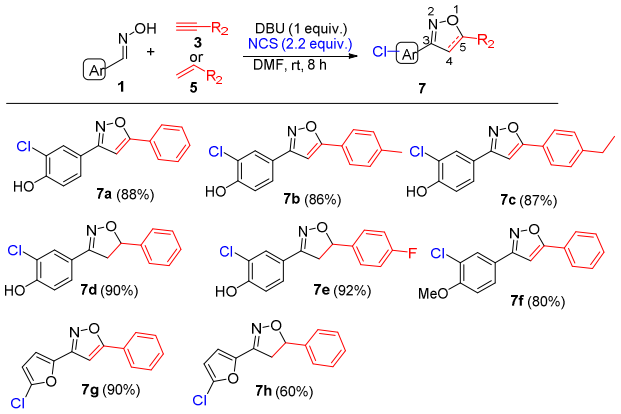

Figure 6. One-pot synthesis of chloro-substituted isoxazoles and isoxazolines. Reagents and conditions: aldoxime (1 equiv.), styrene or alkyne (1.2 equiv.), DBU (1 equiv.), NCS (2.2 equiv.), DMF, 8 h, 60-90%.

Next, we sought to investigate the mechanistic sequence of 1,3-dipolar cycloaddition and ring chlorination (Figure 7) reactions using LCMS analysis. For this, we first performed reaction of aldoxime **1a** with phenylacetylene **3a** under optimized reaction conditions (1.2 equiv NCS). The LCMS chromatogram after 30 min reaction time (figure 7a) indicated formation of desired product **4a** (t_R = 9.4 min). However, with the use of 2.2 equiv NCS, the LCMS chromatogram after 40 min indicated formation of chlorinated isoxazole **7a** (t_R = 10.5 min) along with product **4a** (t_R = 9.4 min). Further, when this reaction was monitored after 8 h, the LCMS chromatogram showed solely the formation of chlorinated product **7a**. This study indicated that the chlorination reaction must be occuring after formation of isoxazole skeleton. In order to further understand the other possibility of first chlorination and then 1,3-dipolar cycloaddition, we treated aldoxime **1a** with 2.2 equiv of NCS and stirred for 8 h, which indicated formation of ring-chlorinated aldoxime only in 15%, which further indicates that in one-pot tandem protocol, chlorination occurs after 1,3-dipolar cycloaddition reaction.

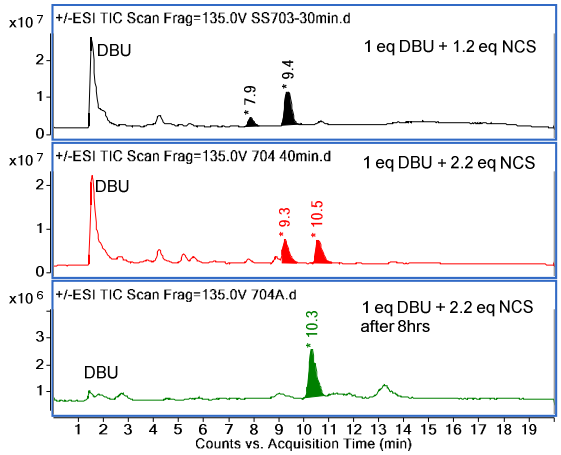

Figure 7. LC chromatograms of reaction of **1a** with **3a** with the change in NCS equivalents. MS spectras are provided in ESI. The products **4a** and **7a** appears at t_R 9.4 and 10.5 min, respectively.

In conclusion, we have developed a new metal-free DBU-promoted synthesis of isoxazole and isoxazolines from aldoximes. Additionally, an interesting one-pot protocol for tandem 1,3-dipolar cycloaddition followed by regioselective ring chlorination has been reported. This methodology was applied to one-pot synthesis of 4-chloro-furyl-isoxazole and pyridine-isoxazole scaffold which are reported to possess potent biological activities.

Experimental Section

General procedure for preparation of isoxazoles 4a-4l, isoxazolines 6a-6q and chlorinated isoxazole/ isoxazoline products 7a-7h. To the stirred solution of aldoximes (100 mg, 1 equiv.) in DMF (3 ml) was added N-chlorosuccinimide (1.2 or 2.2 equiv.) at room temperature and reaction was stirred for 0.5-1 h. Then, DBU (1 equiv.) and styrenes or alkynes (1.2 equiv.) were added and reaction was further stirred for 1-8 h. After completion of the reaction (confirmed by TLC), chilled water (20 ml) was added and product was extracted with EtOAc (3 × 10 ml). The organic layer was collected, dried on anhydrous sodium sulphate and solvent was evaporated on rotary evaporator to get the crude product. The crude product was purified by silica gel (#100-200) column chromatography using 2 to 20% EtOAc: hexane to get pure isoxazoles **4a-4l,** isoxazolines **6a-6q** or chlorinated isoxazole/ isoxazoline products **7a-7h** in 50-90% yield. The spectral data of representative compounds **4a, 6a** and **7a** is shown here. Spectral data of other compounds **4b-4l, 6b-6q** and **7b-7h** is provided in ESI.

*4-(5-Phenylisoxazol-3-yl) phenol (**4a**).*[6] White solid; yield 80%; m. p. 187 – 189 °C ; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.83 (dd, J = 4, 8Hz, 2H), 7.76 (d, J = 8 Hz), 2H), 7.47 (m, 3H), 6.95 (d, J = 8 Hz, 2H), 6.78 (s, 1H); ^{13}C NMR ($CDCl_3$ +CD_3OD, 125 MHz): δ 170.0, 162.9, 158.8, 130.2, 128.9, 128.2, 127.2, 125.7, 120.0, 115.7, 97.3; IR ($CHCl_3$): ν_{max} 3433, 2925, 1631, 1450, 1353, 1095, 1017 cm^{-1}; ESI-MS: *m/z* 238.08 $[M+H]^+$; HRMS: *m/z* 238.0864 calcd for $C_{15}H_{11}NO_2+H^+$ (238.0864).

*3,5-Diphenyl-4,5-dihydroisoxazole (**6a**).*[4a] White solid; yield 85%; m. p. 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.70 (dd, J = 4.0, 8.0 Hz, 2H), 7.30- 7.42 (m, 8H), 5.75 (dd, J = 11.0, 8.3 Hz, 1H), 3.79(dd, J = 16.6, 11.0 Hz, 1H), 3.35 (dd, J = 16.6, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.1, 140.9, 130.2, 129.4, 128.8, 128.2, 126.7, 125.9, 82.6, 43.2; IR ($CHCl_3$): ν_{max} 3433, 2920, 1730, 1446, 1352, 1120, 893, 751, 686 cm^{-1}; ESI-MS: *m/z* 224.10 $[M+H]^+$; HRMS: *m/z* 224.1084 calcd for $C_{15}H_{13}NO+H^+$ (224.1070).

*2-Chloro-4-(5-phenylisoxazole-3-yl)phenol (**7a**).* White solid; yield 88%; m. p. 193-196 °C ; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.89 (d, J = 4.1, Hz, 1H), 7.82-7.84 (m, 2H), 7.68-7.71 (m, 1H), 7.47-7.50 (m, 3H), 7.13 (d, J = 8 Hz, 1H), 6.77(s, 1H), 5.78 (s, 1H); ^{13}C NMR ($CDCl_3$+CD_3OD, 125 MHz): δ 170.3, 161.9, 154.4, 130.3, 128.9, 128.3, 127.1, 126.3, 125.7, 121.0, 116.7, 97.2; IR ($CHCl_3$): ν_{max} 3346, 2922, 2851, 1594, 1422, 1019 cm^{-1}; ESI-MS: *m/z* 272.04 $[M+H]^+$; HRMS: *m/z* 272.0481 calcd for $C_{15}H_{10}ClNO_2+H^+$ (272.0473).

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References and notes

1. For biological activities of isoxazoles and isoxazolines, see: (a) Y. Al-Abed, D. Dabideen, B. Aljabari, A. Valster, D. Messmer, M. Ochani, M. Tanovic, K. Ochani, M. Bacher, F. Nicoletti, C. Metz, V. A. Pavlov, E. J. Miller and K. J. Tracey, *J. Biol. Chem.*, 2005, **280**, 36541-36544; (b) R. Kakarla, J. Liu, D. Naduthambi, W. Chang, R. T. Mosley, D. Bao, H. M. Micolochick Steuer, M. Keilman, S. Bansal, A. M. Lam, W. Seibel, S. Neilson, P. A. Furman and M. J. Sofia, *J. Med. Chem.*, 2014, **57**, 2136–2160; (c) A. P. Kozikowski, *Acc. Chem. Res*, 1984, **17**, 410-416; (d) V. Nair and T. D. Suja, *Tetrahedron*, 2007, **63**, 12247-12275; (e) K. Takenaka, T. Nagano, S. Takizawa and H. Sasai, *Tetrahedron: Asymm.*, 2010, **21**, 379-381; (f) S. Tapadar, R. He, D. N. Luchini, D. D. Billadeau and A. P. Kozikowski, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3023-3026; (g) K. A. El Sayed, P. Bartyzel, X. Shen, T. L. Perry, J. K. Zjawiony and M. T. Hamann, *Tetrahedron*, 2000, **56**, 949-953; (h) M. Gopalakrishnan, J. Ji, C.-H. Lee, T. Li and K. Sippy, B, 2009, WO2009/149135A1 (Abbott Laboratories); (i) P. Proksch, A. Putz, S. Ortlepp, J. Kjer and M. Bayer, *Phytochem Rev*, 2010, **9**, 475-489; (j) V. Jager and P. A. Colinas, in: Synthetic applications of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products, eds. A. Padwa and W. H. Pearson, Wiley: Hoboken, NJ, 2002, pp. 361-472.

2. For synthetic reports on isoxazoles, see: (a) M. P. Bourbeau and J. T. Rider, *Org. Lett.*, 2006, **8**, 3679-3680; (b) L. Cecchi, F. De Sarlo and F. Machetti, *Eur. J. Org. Chem.*, 2006, **2006**, 4852-4860; (c) C.-y. Chen, T. Andreani and H. Li, *Org. Lett.*, 2011, **13**, 6300-6303; (d) J. A. Crossley and D. L. Browne, *J. Org. Chem.*, 2010, **75**, 5414-5416; (e) E. Gayon, O. Quinonero, S. Lemouzy, E. Vrancken and J.-M. Campagne, *Org. Lett.*, 2011, **13**, 6418-6421; (f) O. Jackowski, T. Lecourt and L. Micouin, *Org. Lett.*, 2011, **13**, 5664-5667; (g) S. Minakata, S. Okumura, T. Nagamachi and Y. Takeda, *Org. Lett.*, 2011, **13**, 2966-2969; (h) M. S. Mohamed Ahmed, K. Kobayashi and A. Mori, *Org. Lett.*, 2005, **7**, 4487-4489; (i) C. Praveen, A. Kalyanasundaram and P. T. Perumal, *Synlett*, 2010, **2010**, 777-781; (j) S.-R. Sheng, X.-L. Liu, Q. Xu and C.-S. Song, *Synthesis*, 2003, 2763-2764; (k) B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan and T. G. Driver, *Org. Lett.*, 2010, **12**, 2884-2887; (l) S. Tang, J. He, Y. Sun, L. He and X. She, *Org. Lett.*, 2009, **11**, 3982-3985; (m) M. Ueda, A. Sato, Y. Ikeda, T. Miyoshi, T. Naito and O. Miyata, *Org. Lett.*, 2010, **12**, 2594-2597; (n) J. P. Waldo and R. C. Larock, *J. Org. Chem.*, 2007, **72**, 9643-9647; (o) B. Willy, F. Rominger and T. J. J. Müller, *Synthesis*, 2008, 293-303.

3. (a) S. B. Bharate, A. K. Padala, B. A. Dar, R. R. Yadav, B. Singh and R. A. Vishwakarma, *Tetrahedron Lett.*, 2013, **54**, 3558-3561; (b) T. V. Hansen, P. Wu and V. V. Fokin, *J. Org. Chem.*, 2005, **70**, 7761-7764; (c) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2004, **127**, 210-216.

4. (a) A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev and V. V. Zhdankin, *Org. Lett.*, 2013, **15**, 4010-4013; (b) A. Yoshimura, C. Zhu, K. R. Middleton, A. D. Todora, B. J. Kastern, A. V. Maskaev and V. V. Zhdankin, *Chem. Commun.*, 2013, **49**, 4800-4802; (c) B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh and M. A. Ciufolini, *Org. Lett.*, 2009, **11**, 1539-1542; (d) A. M. Jawalekar, E. Reubsaet, F. P. J. T. Rutjes and F. L. van Delft, *Chem. Commun.*, 2011, **47**, 3198-3200.

5. R. D. Richardson, J. M. Zayed, S. Altermann, D. Smith and T. Wirth, *Angew. Chem. Int. Ed.*, 2007, **46**, 6529–6653.

6. M. A. Weidner-Wells, T. C. Henninger, S. A. Fraga-Spano, C. M. Boggs, M. Matheis, D. M. Ritchie, D. C. Argentieri, M. P. Wachter and D. J. Hlasta, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4307–4311.

7. D. E. Kizer, R. B. Miller and M. J. Kurth, *Tetrahedron Lett.*, 1999, **40**, 3535-3538.

8. W. Chen, J. Cui, Y. Zhu, X. Hu and W. Mo, *J. Org. Chem.*, 2012, **77**, 1585−1591.

9. F. Wang, S. Cai, Z. Wang and C. Xi, *Org. Lett.*, 2011, **13**, 3202–3205.

10. K. E. Larsen and K. B. G. Torssell, *Tetrahedron*, 1984, **40**, 2985-2988.