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ACTIVITY OF DABCO: CATALYTIC SCOPE IN ORGANIC SYNTHESIS

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Abstract: 1,4-DiAzaBiCyclo[2.2.2.]octane (DABCO) is a good neucleophile and base in number of organic reactions and gaining particular importance as catalyst in synthetic organic chemistry. Catalytic applications of DABCO in various reactions such as cycloaddition reaction, coupling reaction, Baylis-Hillman reaction, Henry reaction, ring opening reaction etc. are noteworthy in synthesis of novel organic scaffold. In this article it is tried to overview the recent development of DABCO catalysed reaction as well as its use in heterocyclic synthesis.

Keywords: DABCO; catalyst; Cycloaddition; coupling reaction; Baylis-Hillman reaction, heterocycles, Henry reaction

1. Introduction:

1,4-DiAzaBiCyclo[2.2.2.]octane (DABCO) also known as triethylenediamine is a bicyclic compound with molecular formula $N_2C_6H_{12}$ (Figure1). It is a tertiary amine having high nucleophilic character and act as Lewis base in variety of reactions leading to important organic scaffolds[1]. This chapter includes a brief overview of general reactions namely cycloaddition reaction, coupling reaction, Baylis-Hillman reaction, Henry reaction, ring opening reaction as well as reactions involving the formation of novel heterocycles where DABCO is used as catalyst.

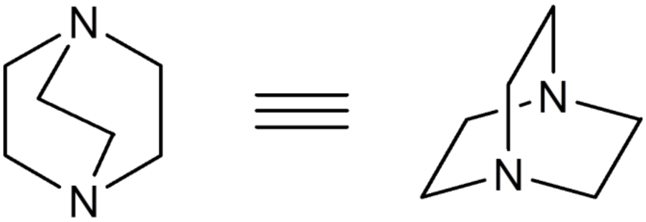
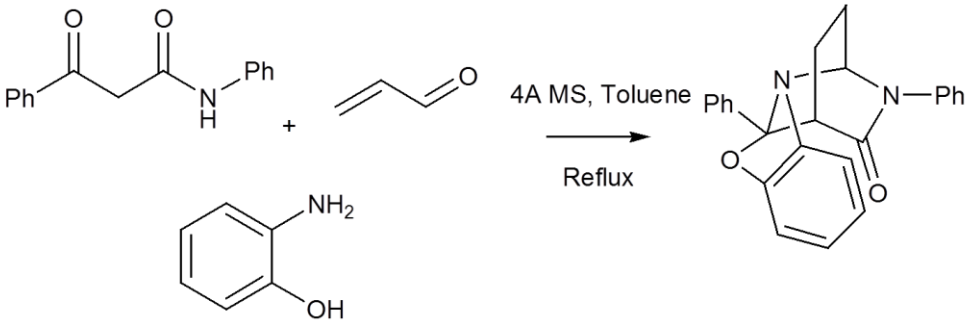


Figure 1: 1,4-DiAzaBiCyclo[2.2.2.]octane

From the single crystal X-ray diffraction studies the crystal structure of DABCO is studied [1] and it is observed that the perhydrate of DABCO is a helical chain of hydrogen peroxide molecules forming a 3-D network by interaction with the diamine whereas in monohydrate, water and diamine molecules are alternately linked. Similarly in the hexahydrate, cyclic water aggregates create cavities which are occupied by DABCO molecules. However the investigation of the crystal structure of DABCO salts of the 1,2-PPA and 1,4-PPA reveals the presence of an interesting hydrogen bond network (3D in 1,2-PPA and 2D in 1,4-PPA respectively) in the solid state.[2]

Furthermore it can be mentioned that polyfunctionalized DABCO core can be prepared by multi-component reaction of acrolein, *ortho*-aminophenol and 2-benzoylacetanilide using ionic liquid as solvent (Scheme 1).[3]



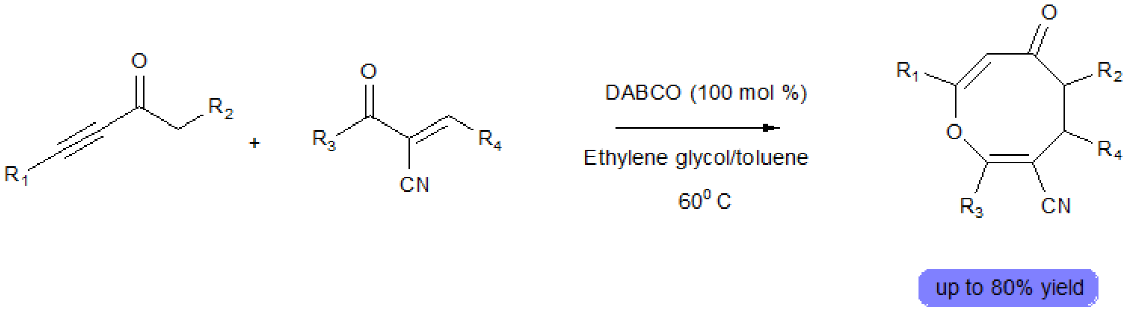
Scheme 1

2. Applications OF DABCO:

2.1. Cylcoaddition reactions:

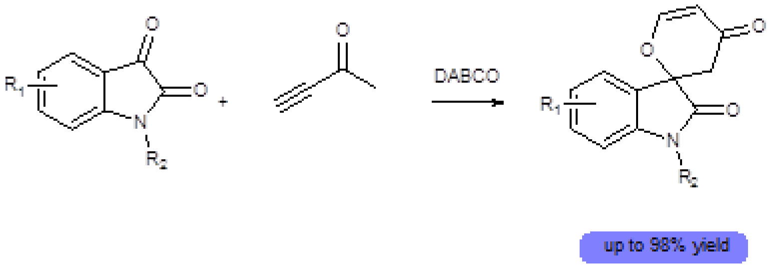
Over the last decade, cycloaddition reaction has received considerable attentions while growing emphasis on synthetic green methodologies, as it involves the formation of cyclic compounds with 100% atom economy and several efforts [4] are being made to utilize this reaction strategy for generation of hetero- and carbocycles. The base promoted cycloadddition reaction was much explored after the pioneering work of Schollkopf [5] and studies have been done afterwards on the cycloadditon reactions involving DABCO as one of the prominent Lewis bases.

DABCO mediated domino [4+4] cycloadddition reaction leads to the formation of eight-membered cyclic ether derivatives [6] in good yields. The reaction is investigated with ynones and α-cyano-α,β-unsaturated ketones as substrates and under mild conditions resulted good to moderate yields (Scheme 2). This protocol provides a simple and atom-economic alternative for the formation cyclic ethers.

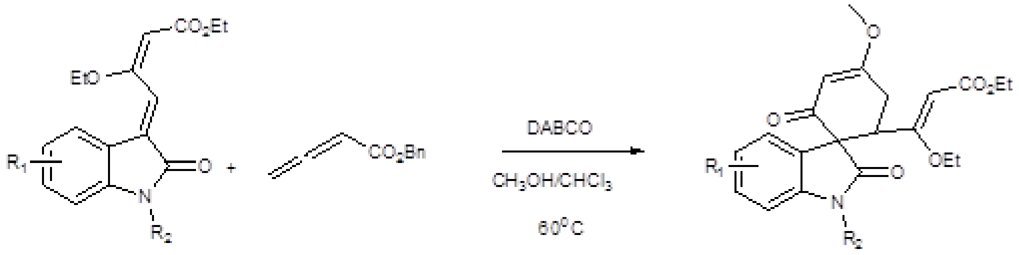


Scheme 2

Spirooxindole ring system is present in many natural products and compounds exhibit intriguing biological activities containing spirooxindole core system. To design an efficient synthetic method for spirooxindole scaffold is still a challenge for organic chemist. However, DABCO catalyzed [4+2] cycloadditon can be employed as an efficient route for the formation of spirooxindole ring using isatins and but-3-yn-2-one [7] (Scheme 3). Similar cycloaddition reaction with variation in the method by using methyleneoxindoles and allenoates as starting materials leads to the formation of spirooxindole in good yields [8] (Scheme 4).

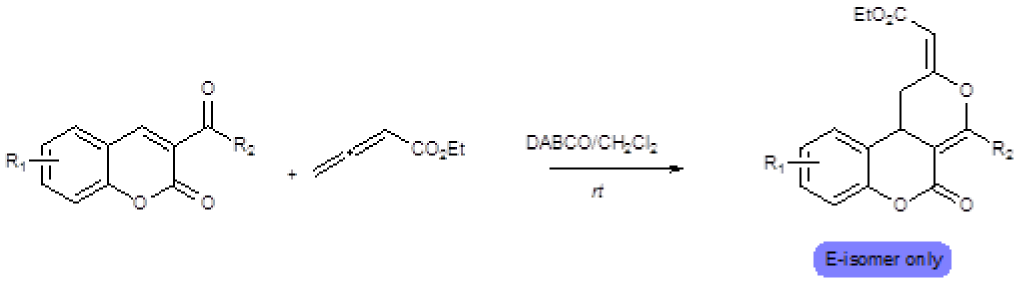


Scheme 3



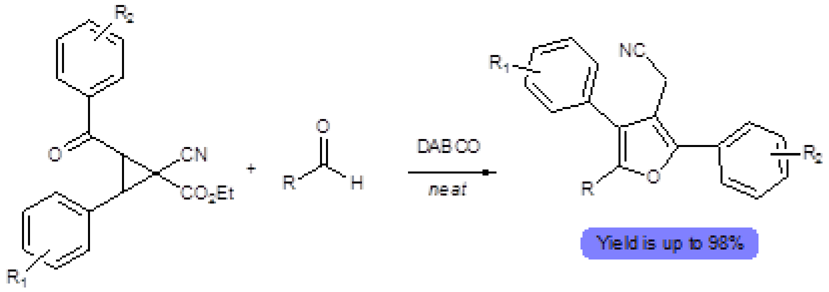
Scheme 4

Dihydropyran-fused chromen-2-ones are readily obtained by [4+2] cycloaddition reaction of 3-acyl-2H-chromen-ones and ethyl 2,3-butadienoate catalyzed by DABCO (Scheme 5). The regio-and stereo-selectivities of the products obtained can be controlled by the mode of reaction and variation in catalyst [9].



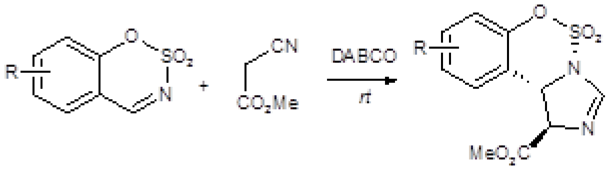
Scheme 5

In a similar reaction, DABCO mediated [3+2] cycloadditon of cyclopropanes and aldehyde affords substituted furan derivatives [10]. The reaction is studied in various solvents as well as basic conditions and substituted furan derivatives are obtained in excellent yields when the reaction is performed under solvent free condition (Scheme 6).



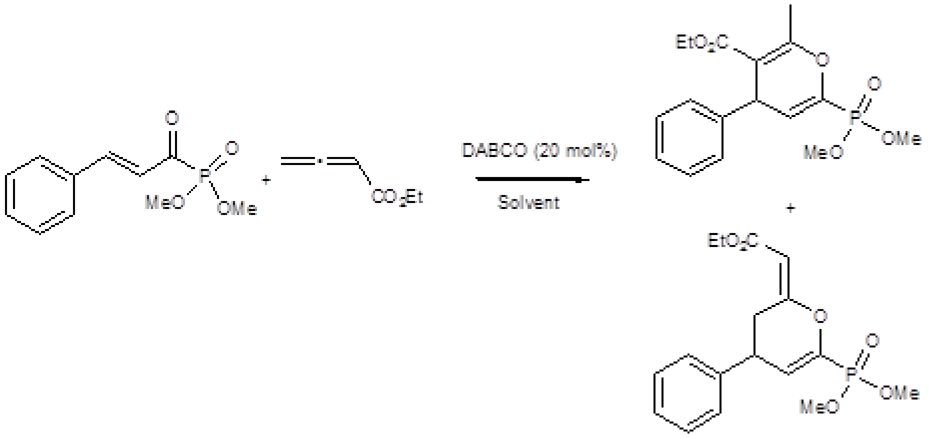
Scheme 6

DABCO catalysed cycloaddition reaction can be performed effectively for the synthesis of imidazoline derivatives. Sulfamate-fused 2-imidazoline is obtained in moderate to excellent yields[11] by [3+2] cycloaddition of sulfamate-derived cyclic imines and isocyanoacetates mediated by DABCO (Scheme 7).



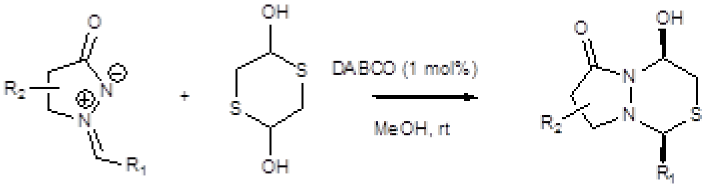
Scheme 7

DABCO catalyzes [4 + 2] cycloaddition of β,γ-unsaturated α-ketophosphonates or β,γ-unsaturated α-ketoesters with allenic esters efficiently yielding the corresponding tetrahydropyran and dihydropyran derivatives in good to excellent yields. [12] This reaction shows moderate to good regioselectivities under mild conditions (Scheme 8).



Scheme 8

Again, [3+3] cycloaddition of 1,4-dithiane-2,5-diol with azomethine imines catalyzed by DABCO yields six-membered dinitrogen-fused heterocycles in good yields (Scheme 9). [13] An excellent diastereoselectivity is observed in the reaction and it is assumed that the anomeric effect of the substrates controls this diastereoselectivity.

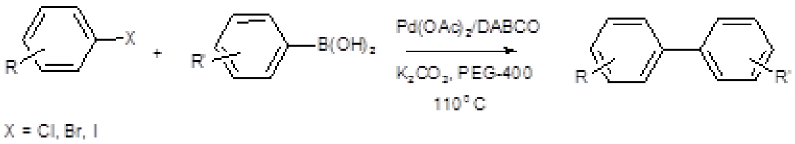


Scheme 9

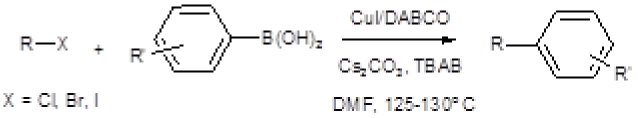
2.2. Coupling reactions:

Nowadays transition-metal-catalysed coupling reactions are earning much attraction as they provide interesting methodologies for the formation of C-C and C-heteroatom bonds. In continuation of the modifications for transition-metal-catalysed methodologies, cross coupling reactions are gaining particular interest [14]. Following this trend number of cross coupling reactions have been developed with improved catalytic system. In this regard investigations of catalytic activities of Lewis bases are carried on and variety of reactions were well studied involving DABCO as Lewis base.

Pd(OAc)$_2$/DABCO is an efficient catalytic system for the Suzzuki-Miyaura cross-coupling reaction [15]. This catalytic system provides a smooth accomplishment of the reaction with the advantage that it can be recycled and reused without any lose of catalytic activity (Scheme 10). The catalytic system in Suzzuki-Miyaura reaction is further modified using DABCO as ligand and employing Cu [16] instead of Pd (Scheme 11). However, CuI/DABCO system is also effective for Sonogashira cross-coupling reaction yielding moderate to excellent yield.

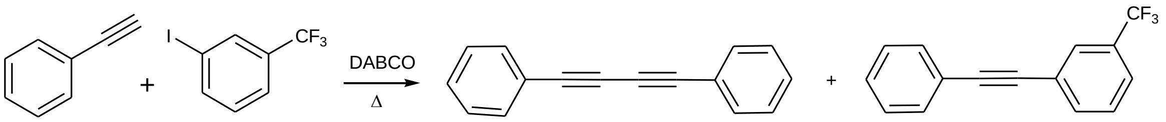


Scheme 10



Scheme 11

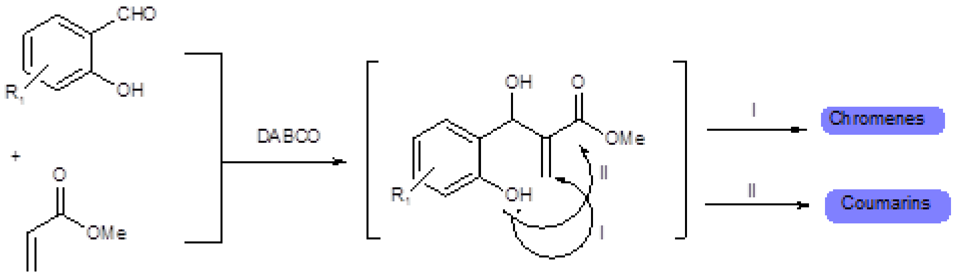
DABCO can be used as prominent catalyst without using Cu under solvent free condition for the Sonogashira cross-coupling reaction [13] (Scheme 12). The yield of the reaction is up to 90% with different electron-deficient aryl halides affording cross-coupling alkyne products. Recently, a DABCO catalysed silica-copper(I) nanocatalytic system is reported [14] for pd-free Sonogashira cross-coupling reaction. This catalytic system is efficient and recyclable for the C–C bond formation of aryl halides with phenylacetylene through Sonogashira coupling.



Scheme 12

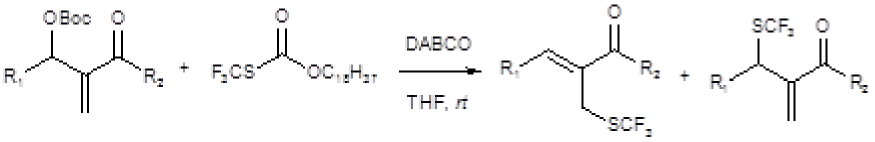
2.3. Baylis-Hillman reaction:

The most important application of DABCO as catalyst is in the Baylis-Hillman reaction. This reaction is a variation of aldol condensation which is an important methodology for the formation hydroxy carbonyl compounds. The Baylis-Hillman reaction involves the conjugate addition of DABCO to acrylate followed by attack to aldehyde and the reaction is applicable for the synthesis of novel heterocycles. For example, Coumarin and chromene derivatives can be synthesised in good yields [15] applying Baylis-Hilman reaction using 2-hydroxybenzaldehyde and methyl acrylate as substrates in presence of DABCO (Scheme 13).



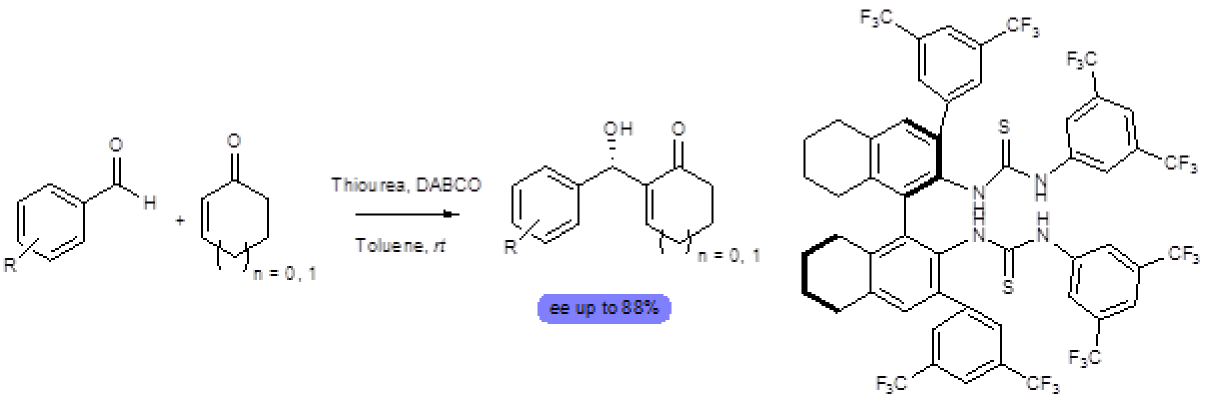
Scheme 13

Nucleophilic trifluoromethylthiolation reaction can be also performed [16] using Baylis-Hillman reaction in the presence of DABCO. O-octadecyl-Strifluorothiolcarbonate is used as the nucleophilic tifluoromethylthiolation reagent in this reaction (Scheme 14).



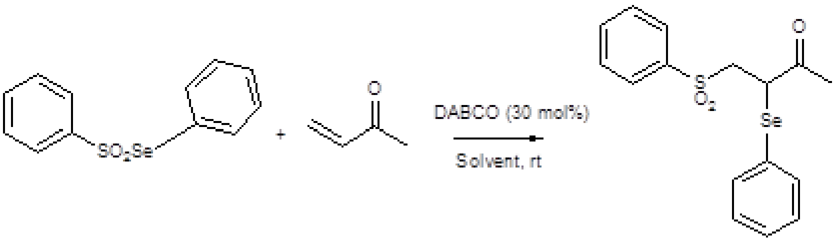
Scheme 14

DABCO cataylsed Baylis-Hillman reaction can be employed for asymmetric synthesis with high enantioselectivity using chiral reagent. Reaction of 2-cyclohexen-1-one with different aromatic aldehydess using chiral thiourea organocatalyst [17] results the steriogenic hydroxyl ketone with *ee* up to 88% (Scheme 15).



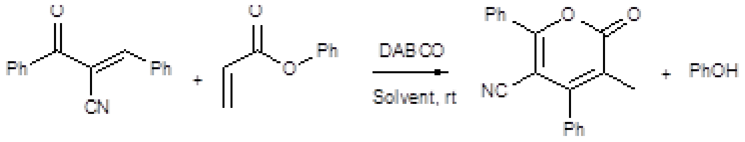
Scheme 15

It can be mentioned that the addition of selenosulfonates to carbon–carbon unsaturated bonds has been known to proceed in the presence of Lewis acid BF_3·OEt or through a radical reaction pattern. However, DABCO catalyzes the Baylis–Hillman reaction of selenosulfonates and methyl vinyl ketone giving the corresponding adduct in good yields at room temperature (Scheme 16). [18]



Scheme 16

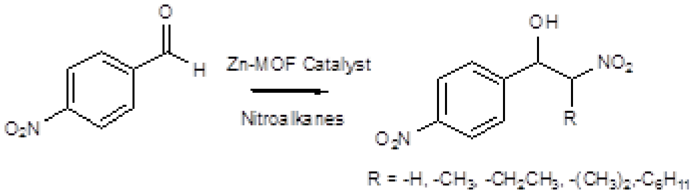
Among the carbon–carbon bond-forming reaction the Rauhut–Currier (RC) reaction, also known as vinylogous Morita–Baylis–Hillman (MBH) reaction is a remarkable reaction. The intermolecular RC reaction employing a-cyano-a,ß-unsaturated ketones as activated alkenes for the synthesis of dihydropyrans, uses DABCO as catalyst (Scheme 17). [19]



Scheme 17

2.4. Henry reaction:

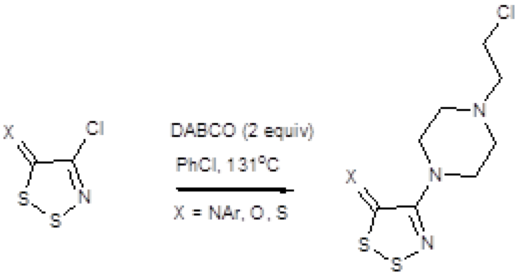
Henry reaction is a special nitroaldol reaction where nitrobenzaldehyde reacts with nitroalkanes. In this reaction metal-organic framework can be used as effective catalyst. In Zn-metal-organic framework containg DABCO involve one N atom instead of the two available N atoms to coordinate Zn. This Zn-MOF catalyzes the Henry reaction of 4-nitrobenzaldehyde and nitroalkanes in a molecular size selective manner [20] with Small nitroalkanes give rise to higher conversion than larger ones (Scheme 18).



Scheme 18

2.5. Ring opening reaction:

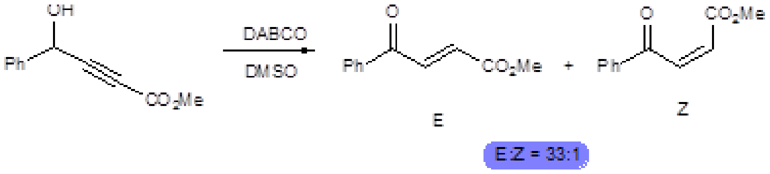
As DABCO core contains two nitrogen atom with two lone pairs, it is strongly neucleophilic. Employing this neucleophilicity, ring opening reaction of DABCO gives an interesting strategy for the synthesis 2-substituted ethylpiperazine group. [21] In this regard it can be mentioned that the reaction of 4-chloro-5H-1,2,3-dithiazoles with DABCO leads to the facile formation of piperazin-1-yl- dithiazol derivatives (Scheme 19). [22]



Scheme 19

2.6. Isomerisation reaction:

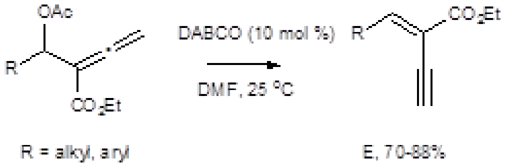
DABCO catalyzes isomerisation reaction of alkyne to alkene efficiently. Thus the isomerisation reaction of γ-hydroxy-α,β-acetylenic esters to γ-oxo-α,β-trans-alkenyl esters is performed efficiently using DABCO as catalyst (Scheme 20). [23] The transformation is however regioselctive giving both E and Z isomer of the product.



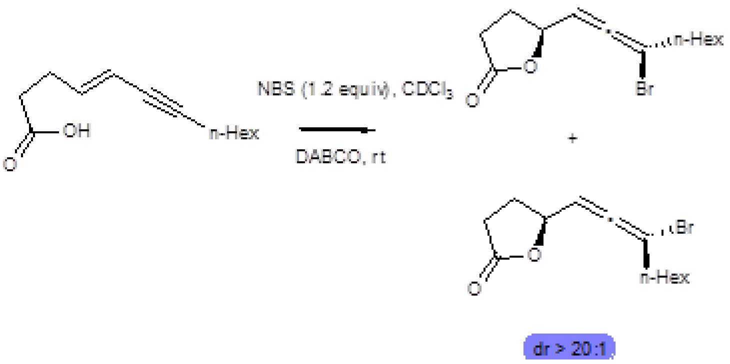
Scheme 20

2.7. Stereoselective ester formation reactions:

The stereoselective reaction involving the formation of esters; it may be α, β-unsaturated esters or cyclic ester catalysed by DABCO leads the products in good yields. Thus, (E)α-ethynyl- α, β-unsaturated esters are obtained from allenyl acetates using DMF as solvent under catalytic condition of DABCO yielding stereoselectively E-isomer (Scheme 21). [24] Again enyne bromolactonization of E and Z isomer of enynic acid catalyzed by DABCO gives lactone having substituted allene with syn stereoselectivity (Scheme 22). [25]



Scheme 21

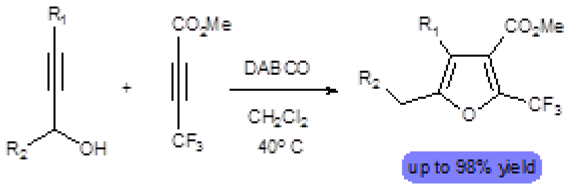


Scheme 22

2.8. Synthesis of novel heterocycles:

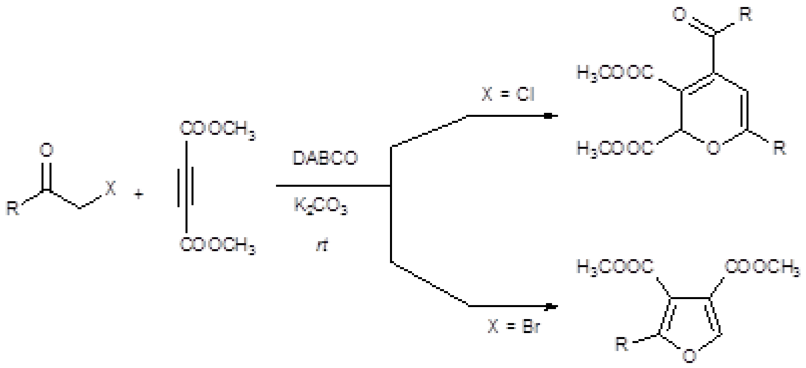
The majority of biologically active compounds are comprised of heterocycles. Among the heterocyclic compounds oxygen and nitrogen containing heterocycles such as Furan, pyran, Chromene, pyranochromene, pyrazole, quinolines, quinazolines are growing particular interest as these rings are found as main sub-unit in natural products such as alkaloids, flavonoids, tocopherols etc. Moreover, the compounds contaning these rings are found to have diverse biological activities. [26, 27] Thus the prevalence of these heterocycles has motivated several research groups for extensive investigations and numbers of methodologies for DABCO catalysed comprehensive synthesis novel heterocycles have been extensively developed.

When propargyl alcohol is treated with methyl 2-perfluoroalkynoate using DABCO as base and DCM as solvent [28], it affords trifluoromethylated furans in excellent yield (Scheme 23). The reaction proceeds through Michael addition followed by Claisen cyclization process.



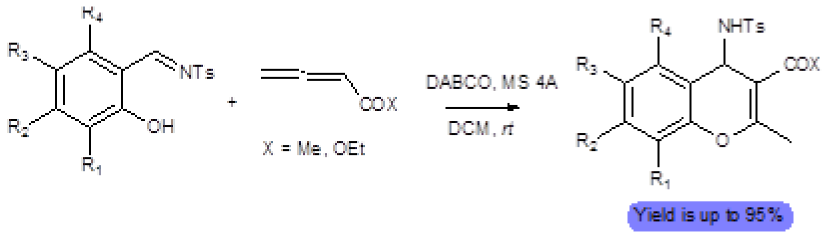
Scheme 23

Again, reactions of α-halo carbonyl compounds with alkyes having electron withdrawing groups such as dimethylacetylenedicarboxylate in presence of K_2CO_3 and DABCO result substituted furans and pyrans [29] (Scheme 24).



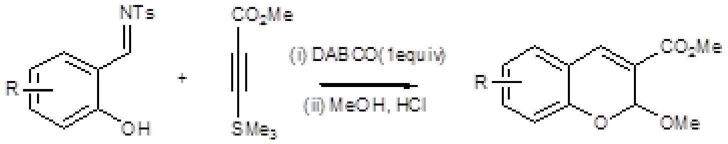
Scheme 24

DABCO mediated reaction of allenic esters and ketones with salicyl N-Tosylimines affords highly functionalized chromenes in good yields [30]. The reaction is carried out in room temperature (Scheme 25).



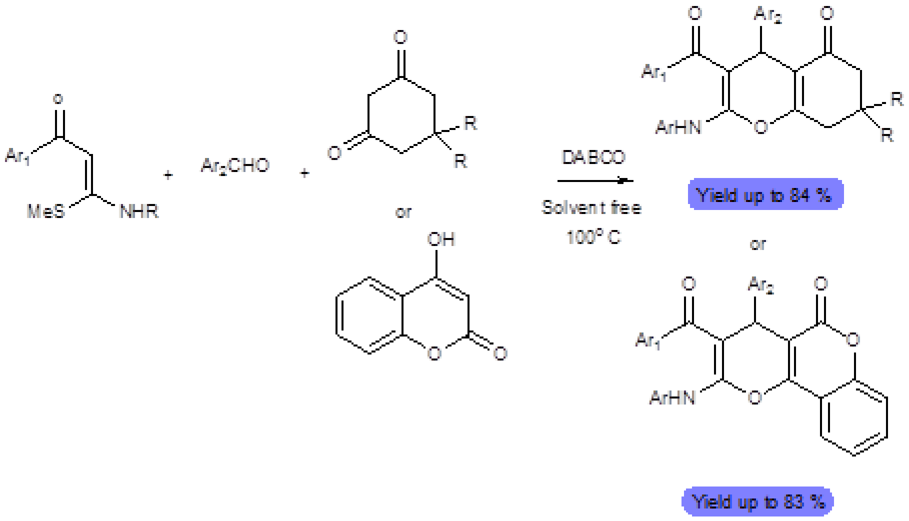
Scheme 25

Again, Chromene is obtained in a reaction of salicyl *N*-tosylimine and methyl 3-trimethylsilylpropiolate under catalytic condition of DABCO (Scheme 26). [31] The reaction proceeds through a three component coupling fashion where salicyl *N*-tosylimine act as bifunctional substrate.



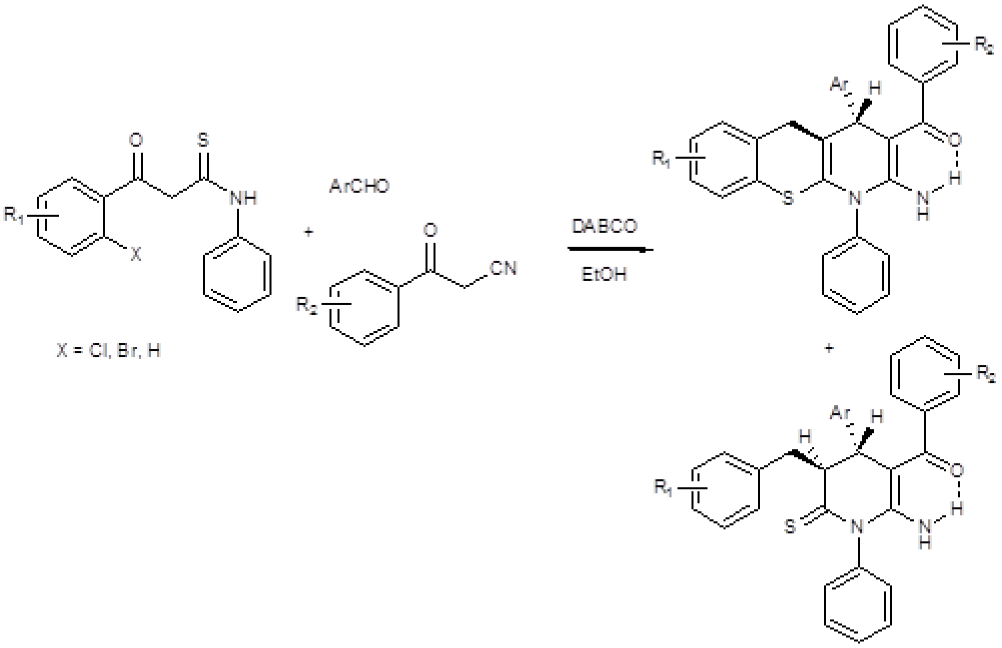
Scheme 26

Chromen-5-ones and Pyrano[3,2-*c*]chromen-5-ones can be synthesized by one-pot three-component coupling reaction [32] in presence of DABCO under solvent-free conditions (Scheme 27). Reaction of α-oxoketene-*N*,*S*-arylaminoacetals, aromatic aldehydes, and dimedone results chromen-5-ones. However the use of 4-hydroxycoumarin instead of dimedone in this reaction affords Pyrano[3,2-*c*]chromen-5-ones in high yields.



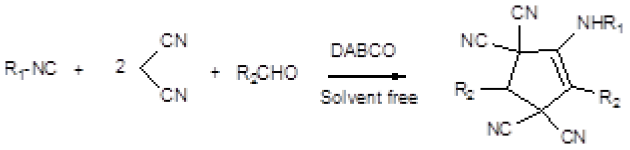
Scheme 27

DABCO catalyzes a three component [3+2+1] annulation reaction of β-aroylthioacetanilides, aldehyde and aroyl acetonitriles. [33] In this reaction 1,2,3,4tetrahydropyridine derivatives or thiochromeno[2,3-b]pyridine derivatives are obtained with high chemo-, stereo, and unusual regioselectivity (Scheme 28).

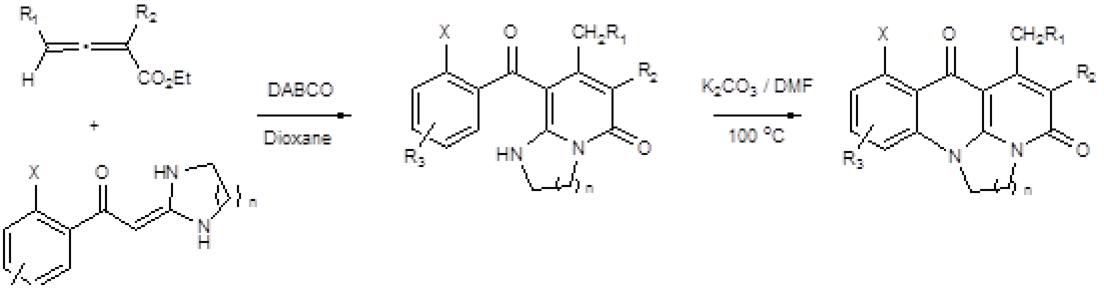


Scheme 28

Again, DABCO mediated multi-component reaction of isocyanides, aldehydes and malononitrile leads to the formation of substituted cyclopentenes (Scheme 29). [34] Morever, DABCO catalyzed tandem annulations reaction of 2-(2-chloroaroyl)methyleneimidazolidines with allenic esters affords functionalized imidazo(pyrido)[1,2-a]pyridines in good yields through subsequent formation of dihydroimidazo[1,2-a]pyridin-5(1H)-one (Scheme 30). [35]

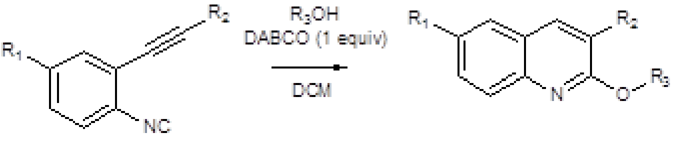


Scheme 29



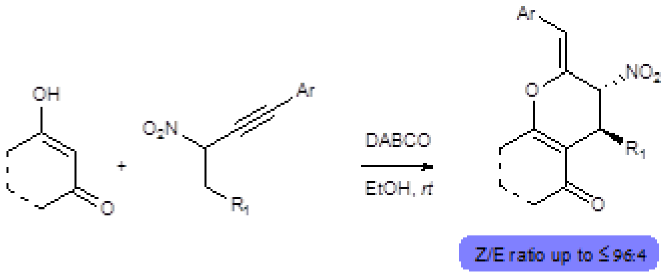
Scheme 30

Nucleophilic addition of DABCO to isocyanide and stepwise cycliztion followed by subsequent substitution of the DABCO moiety with oxygenated nucleophiles results 2-alkoxy- and 2-aroxy-3-substituted quinolines (Scheme 31). [36]



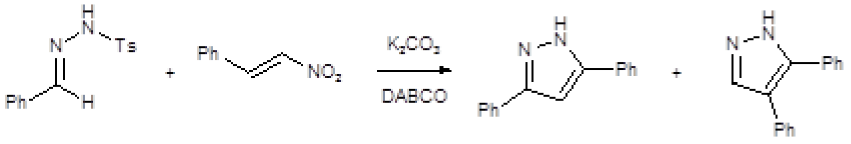
Scheme 31

Stereoselective formation of pyrano[3,2-c]chromenes are achieved by Michael/hydroalkylation reaction [37] of α-arylacetylenylß-arylnitroolefins with enolizable cyclic 1,3 dicarbonyls at room temperature using DABCO as a cheap organocatalyst and ethanol as solvent. The formation of pyrano[3,2-c]chromenes is excellent stereoselective yielding up to =96 : 4 Z/E ratio (Scheme 32).



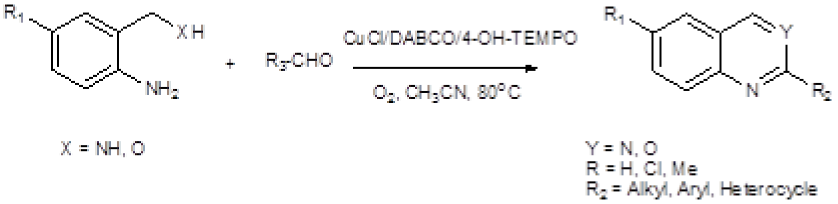
Scheme 32

Facile synthesis of pyrazole can be achieved successfully if tosylhydrazones and nitroalkenes are used as substrates in presence of catalytic amount of DABCO [38] (Scheme 33).



Scheme 33

Moreover, Quinazolines can be synthesized efficiently [39] by one-pot reaction of aldehydes and 2-aminobenzylamines under catalytic condition of CuCl/DABCO (Scheme 34).

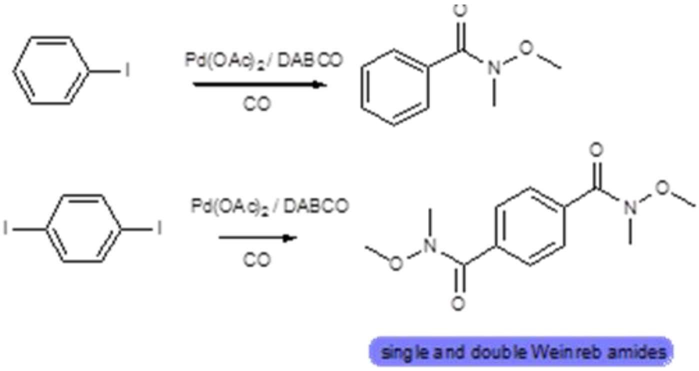


Scheme 34

2.9. Miscellaneous:

Now a day's co-ordination polymer gel is attracking particular interest in supramolecular chemistry as it has unusual functional properties such as emission [40], absorption [41], catalytic behaviour [42] etc. and it can be obtained by incorporation of metal in organic gelator. A novel three-component gel is reported recently [43] by gelation of Cu^{2+} and Fe^{3+} coordination polymers containing succinic acid and DABCO.

DABCO in combination with $Pd(OAc)_2$ is an efficient catalytic system for the synthesis of single and double Methoxy-N-methyl amides (Weinreb amides). [44] Weinreb amides are important scaffolds in synthetic organic chemistry as it is a chief precursor for the construction of various functional carbonyl compounds.[45, 46] Aminocarbonylation of aryl iodides using DABCO as a stable ligand incorporation with Pd catalyst gives Weirneb amides in good yields (Scheme 35).



Scheme 35

3. Conclusion:

Over the past decades, Lewis base catalysed reactions have considered as powerful tools in rapid construction of organic scaffolds due to their convenience and efficiency. In this regard, 1,4-diazabicyclo[2.2.2.]octane enjoys a broad field as organocatalyst in synthetic organic chemistry since it is a readily available as well as recyclable catalytic system. In this article it is tried to summarize the scope of DABCO as Lewis base catalyst with some relevant important and significant reactions. Research on the usefulness of DABCO in the development of various methodologies is still in progress. It is hoped that more interesting and useful chemical reactions involving this particular system will be explored in near future.

References:

[1] G. Laus, V. Kahlenberg, K. Wurst, T. Lorting and H. Schottenberger, CrystEngComm., 2008, 10, 1638
[2] R. Saravanakumar, B. Varghese and S. Sankararaman, CrystEngComm., 2009, 11, 337
[3] Z-E. Asri, Y. Genisson, F. Guillen, O. Basle, N. Isambert, M. Duque, S. Ladeira, J. Rodriguez, T. Constantieux and J-C. Plaquevent, Green Chem., 2011, 13, 2549
[4] Y.-W. Sun, X.-Y. Guan, M. Shi, Org. Lett., 2010, 12, 5664
[5] R. Meyer, U. Schollkopf and P. Bohme, Liebigs Ann. Chem., 1977, 1183
[6] L. Liang, E. Li, X. Dong and Y. Huang, Org. Lett., 2015, 17, 4914
[7] Q. Wang, Q. Xu and M. Shi, Org. Chem. Front., 2015, 2, 211-215
[8] Y. Liu, Y. Du, A. Yu, H. Mu and X. Meng, Org. Biomol. Chem., 2016, 14, 1226
[9] Y. Wang, Z-H. Yu, H-F. Zheng and D-Q. Shi, Org. Biomol. Chem., 2012, 10, 7739
[10] J. Liu, W. Ye, X. Qing, C. Wang, J. Org. Chem., 2016, DOI: 10. 1021/acs.joc.6b01259
[11] Z. Gao, L. Zhang, Z. Sun, H. Yu, Y. Xiao and H. Guo, Org. Biomol. Chem., 2014, 12, 5691
[12] C. -K. Pei, L. Lei Wu, Z. Lian and M. Shi, Org. Biomol. Chem., 2012, 10, 171
[13] X. Fang, J. Li, H. –Y. Tao, C. –J. Chun-Jiang Wang, Org. Lett., 2013, 15, 5554
[14] S. V. Ley and A. W. Thomas, Angew. Chem. Int. Ed., 2003, 42, 5400
[15] J-H. Li, W-J. Liu and Y-X. Xie, J. Org. Chem., 2005, 70, 5409-5412
[16] J-H. Li, J-L. Li, D-P. Wang, S-F. Pi, Y-X. Xie, M-B. Zhang and X-C. Hu, J. Org. Chem., 2007, 72, 2053
[17] M. Shi and X-G. Liu, Org. Lett., 2008, 10, 1043
[18] Y. L. Shi and M. Shi, Org. Biomol. Chem., 2005, 3, 1620
[19] W. Liu and G. Zhao, Org. Biomol. Chem., 2014, 12, 832
[20] M. Gu, W. S. Kim and S. Huh, Dalton Trans., 2011, 40, 10826
[21] (a) I. Yavari, M. J. Bayat, G. Darjani, M.Tetrahedron Lett., 2014, 55, 5595 (b) N. Maras, S. Polanc and M. Kocevar, Org. Biomol. Chem., 2012, 10, 1300 (c) S. G. Gladstone, W. G. Earley, J. K. Acker and G. S. Martin, Tetrahedron Lett., 2009, 50, 3813 (d) H.-J. Wang, Y. Wang, A. J. Csakai, W. G. Earley and R. J. Herr, J. Comb. Chem., 2009, 11, 355 (e) H.-J. Wang, W. G. Earley, R. M. Lewis, R. R. Srivastava, A. J. Zych, D. M. Jenkins and D. J. Fairfax, Tetrahedron Lett., 2007, 48, 3043
[22] M. Koyioni, M. Manoli and P. A. Koutentis, J. Org. Chem., 2016, 81, 615
[23] J. P. Sonye and K. Koide, Org. Lett., 2006, 8, 199
[24] Y. Choe and P. H. Lee, Org. Lett., 2009, 11, 1445
[25] W. Zhang, H. Xu, H. Xu and W. Tang, J. Am. Chem. Soc., 2009, 131, 3832
[26] B. L. Flynn, E. Hamel and M. K. Jung, J. Med. Chem., 2002, 45, 2670

[27] A. Luth and W. Lowe, Eur. J. Med. Chem., 2008, 43, 1478
[28] Q. Chong, X. Xin, C. Wang, F. Wu, H. Wang, J-C. Shi and B. Wan, J. Org. Chem., 2014, 79, 2105
[29] M. Fan, Z. Yan, W. Liu and Y. J. Liang, Org. Chem., 2005, 70, 8204
[30] Y-L. Shi and M. Shi, Org. Lett., 2005, 7, 3057
[31] Y. Matsuya, K. Hayashi, A. Wada and H. Nemoto, J. Org. Chem., 2008, 73, 1987
[32] J. Zhang, X. Wang, L. He, L. Chen, C.-Y. Su and S. L. James, New J. Chem., 2009, 33, 1070 (b) Y. He, Z. Bian, C. Kang, Y. Cheng and L. Gao, Chem. Commun., 2010, 46, 3532
[33] L. R. Wen, Y. –J. Shi, G. –Y. Liu and M. Li, J. Org. Chem., 2012, 77, 4252
[34] L. R. Wen, M. –C. Lan, W. –K. Yuan and M. Li, Org. Biomol. Chem., 2014, 12, 4628
[35] M. Li, Z.-M. Zhou, L. –R. Wen and Z.-X. Qiu, J. Org. Chem., 2011, 76, 3054
[36] J. Zhao, C. Peng, L. Liu, Y. Wang and Q. Zhu, J. Org. Chem., 2010, 75, 7502
[37] S. Biswas, A. Dagar, S. M. Mobin and S. Samanta, Org. Biomol. Chem., 2016, 14, 1940
[38] M. Tang, W. Zhang and Y. Kong, Org. Biomol. Chem., 2013, 11, 6250
[39] B. Han, X.-L. Yang, C. Wang, Y-W. Bai, T-C. Pan, X. Chen and W. Yu, J. Org. Chem., 2012, 77, 1136
[40] (a) W. L. Leong, A. Y.-Y. Tam, S. K. Batabyal, L. W. Koh, S. Kasapis, V. W.-W. Yam and J. J. Vittal, Chem. Commun., 2008, 3628 (b) W. L. Leong, S. K. Batabyal, S. Kasapis and J. J. Vittal, Chem.–Eur. J., 2008, 14, 8822 (c) S. K. Batabyal, A. M. P. Peedikakkal, S. Ramakrishna, C. W. Sow, J. J. Vittal, Macromol. Rapid Commun., 2009, 30, 1356 (d) S. K. Batabyal, W. L. Leong and J. J. Vittal, Langmuir, 2010, 26, 7464
[41] S. K. Nune, P. K. Thallapally and B. P. McGrail, J. Mater. Chem., 2010, 20, 7623
[42] (a) J. Zhang, X. Wang, L. He, L. Chen, C.-Y. Su and S. L. James, New J. Chem., 2009, 33, 1070 (b) Y. He, Z. Bian, C. Kang, Y. Cheng and L. Gao, Chem. Commun., 2010, 46, 3532
[43] K. Tanaka and T. Yoshimura, New J. Chem., 2012, 36, 1439
[44] S. T. Gadge, B. M. Bhanage, Org. Biomol. Chem., 2014, 12, 5727
[45] M. Sawamura, Y. Nakayama, T. Kato and Y. Ito, J. Org. Chem., 1995, 60, 1727
[46] D. M. Rudzinski, C. B. Kelly and N. E. Leadbeater, Chem. Commun., 2012, 48, 9610