Catal Lett (2012) 142:895–900
DOI 10.1007/s10562-012-0829-x

$LaCl_3 \cdot 7H_2O$ as an Efficient Catalyst for One-Pot Synthesis of Highly Functionalized Piperidines via Multi-component Organic Reactions

Balijapalli Umamahesh · Venkatesan Sathesh · Gunasekar Ramachandran · Munusamy Sathishkumar · Kulatu Sathiyanarayanan

Received: 5 March 2012 / Accepted: 14 April 2012 / Published online: 15 May 2012

Abstract The three-component one-pot synthesis of highly functionalized piperidine derivatives was carried out by condensing 1,3-dicarbonyl compounds with aromatic aldehydes and aniline using a catalytic amount (10 mol%) of $LaCl_3 \cdot 7H_2O$ in methanol at room temperature. The main features of current protocol include easy work up, mild reaction conditions, good yields and high atom economy.

Keywords One-pot condensation · Lanthanum chloride heptahydrate · Aza Diels–Alder reaction · Knoevenagel condensation · Functionalized piperidines

1 Introduction

As an important aspect of synthetic organic chemistry, multi-component organic reactions (MCRs) are among the most prosperity reaction classes. 1,3-Dicarbonyl compounds are one of the most multifaceted reagents to be used in MCRs because of the high reactivity of enaminones in both keto and enol forms, which are very advantageous to construct useful bioactive heterocycles [1, 2]. MCRs offer a highly valuable synthetic protocol for the construction of highly complex molecules with minimum number of synthetic steps. Wu et al. [3] has described the synthesis of naphthyridine derivatives in which thirteen bonds were cleaved and twelve new bonds were constructed through one-pot cascade reaction, while only two molecules of H_2O were removed. In most of the situations a single product was obtained from three or more different, willingly available starting materials in an illustrious synthetic manner through MCRs [4]. The beneficial effects of these MCRs over the conventional synthesis are shorter reaction time, eco friendliness, cost effectiveness, high atom economy, inexpensive purification and no necessity for protection and deprotection process [5, 6]. Recently, Lewis acids catalyzed Michael addition of Schiff base to enaminones has attracted great attention of synthetic chemists [7, 8].

Poly functionalized piperidines are widely distributed in naturally occurring monocyclic and bicyclic alkaloids and synthetic drugs [9]. A variety of structural features surrounded the naturally occurring and synthetically prepared piperidines, among them many exhibit significant biological properties including anti-HIV, anticancer, antimycobacterial, antimicrobial, antimalarial, antiinflammatory, antiinsecticidal and they are potent inhibitors for many biological systems [10–14]. Much considerable efforts have been focused on the synthetic methods and some of the synthetic routes have been recommended for the synthesis of highly substituted piperidines essentially intramolecular Mannich reaction [15], cyclohydrocarboxylation [16], aziridine ring expansion [17], radical cyclization [18], domino reaction [19], Diels–Alder reaction [20], imino Diels–Alder reaction [21] and domino imino-aldol-aza-Michael addition [22]. Recently one-pot synthesis of these scaffolds has been achieved by employing $InCl_3$ [23], bromodimethylsulfonium bromide [24], L-proline/TFA [25], tetrabutylammonium tribromide [26], molecular I_2 [27], CAN [28], $ZrOCl_2 \cdot 8H_2O$ [29], picric acid [30], thiourea dioxide (TUD) [31], BF_3-SiO_2 [32], VCl_3 [33] and

Electronic supplementary material The online version of this article (doi:10.1007/s10562-012-0829-x) contains supplementary material, which is available to authorized users.

B. Umamahesh · V. Sathesh · G. Ramachandran · M. Sathishkumar · K. Sathiyanarayanan (✉)
Chemistry Division, School of Advanced Sciences, VIT University, Vellore 632014, India
e-mail: sathiya_kuna@hotmail.com

$Bi(NO_3)_3{\cdot}5H_2O$ [34] as efficient catalysts. The above deliberated methods have some disadvantages such as the use of expensive and excess amount of catalysts. Efficacious new approaches for the preparation of chemically and biologically active complex molecules are of great significance with simple mechanism and good selectivity.

Nowadays lanthanides including lanthanum [35], cerium [36], samarium [37] and ytterbium [38] have been employed as efficient catalysts for a wide variety of synthetic reactions. Jun Lu et al. [39] has described an efficient one-pot synthesis of 3,4-dihydropyrimidinones using lanthanum chloride heptahydrate as catalyst from an aldehyde, β-keto ester and urea or thiourea in ethanol. In continuation of this, here we report the one-pot efficient synthesis of highly functionalized piperidines using 10 mol% of $LaCl_3{\cdot}7H_2O$ as a catalyst in a three-component intramolecular aza Diels–Alder reaction.

2 Result and Discussion

For the initial optimization of the reaction conditions and the identification of the suitable solvent and effective reaction conditions, ethyl acetoacetate, benzaldehyde, aniline and 10 mol% of catalyst was selected as prototype. Among the chosen solvents MeOH was the best for the synthesis of tetrahydropyridines showed in Table 1. Although acetonitrile, chloroform and dichloromethane allowed the reaction at a faster rate, the yield was less than that obtained using MeOH as solvent. THF and ethyl acetate gave low yields and no desired product was obtained with water.

By screening a wide range of catalysts, we found out that the product 5a could be obtained in good yields ranging from 20 to 83 % in different mole ratios of $LaCl_3{\cdot}7H_2O$ (1, 2, 5, 10 and 15 mol%) and the results are summarized in Table 2. Better yields were obtained up to 83 % by carrying out the reaction using 10 mol% of $LaCl_3{\cdot}7H_2O$ in MeOH as solvent. The reaction takes place efficiently in an open air system and it does not require any special apparatus like Schlenk system. When the reaction was carried out at reflux conditions, there was no significant change in yields and time (Entry 16, Table 2). Primary screening studies of a variety of catalysts also revealed that lanthanum oxide and silica chloride also act as catalyst. La_2O_3 (10 mol%) and silica chloride (10 mol%) were employed as catalysts for the three-component reaction but moderate yields were obtained. Lower yields were obtained with the use of NH_4OAc and ammonium molybdate.

A wide range of aromatic aldehydes and amines were subjected to react with 1,3-dicarbonyl compounds in the presence of catalytic amount of $LaCl_3{\cdot}7H_2O$ and the results are summarized in Table 3. A variety of aromatic aldehydes possessing electron withdrawing and electron donating groups at different positions on the aromatic ring,

Table 1 Initial solvent effect studies for synthesis of tetrahydropyridines with 10 mol% catalyst

Entry	Solvent	Catalyst	Time (h)	Yield (%)[a]
1	CH_3CN	$LaCl_3{\cdot}7H_2O$	3	74
2	CH_2Cl_2	$LaCl_3{\cdot}7H_2O$	2.5	76
3	$CHCl_3$	$LaCl_3{\cdot}7H_2O$	3	72
4	EtOAc	$LaCl_3{\cdot}7H_2O$	10	44
5	MeOH	$LaCl_3{\cdot}7H_2O$	3	83
6	EtOH	$LaCl_3{\cdot}7H_2O$	4	76
7	i-PrOH	$LaCl_3{\cdot}7H_2O$	6.5	70
8	THF	$LaCl_3{\cdot}7H_2O$	8	59
9	H_2O	$LaCl_3{\cdot}7H_2O$	12	Traces
10	MeOH	SiO_2Cl	3	71
11	CH_3CN	SiO_2Cl	4.5	66
12	$CHCl_3$	SiO_2Cl	4	74

Conditions: ethyl acetoacetate (0.5 mmol), benzaldehyde (1 mmol), aniline (1 mmol) and 10 mol% $LaCl_3{\cdot}7H_2O$ in 5 ml solvent, stirring in room temperature

[a] Isolated yields

Table 2 Screening of catalysts for the one-pot synthesis of tetrahydropyridines

Entry	Catalyst (mol%)	Time (h)	Yield (%)[a]
1	NH_4OAc (10 mol%)	24	46
2	$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (10 mol%)	24	32
3	$AlCl_3$ (10 mol%)	24	24
4	Triethyl amine (10 mol%)	24	Traces
5	Li_2O_3 + L-proline (10 + 5 mol%)	24	40
6	Al_2O_3 acidic (10 mol%)	24	35
7	Al_2O_3 basic (10 mol%)	24	29
8	$ZnCl_2$ (10 mol%)	24	41
9	$FeCl_3$ (10 mol%)	24	32
10	La_2O_3 (10 mol%)	18	65
11	SiO_2Cl (10 mol%)	3.5	68
12	$LaCl_3{\cdot}7H_2O$ (1 mol%)	3.5	20
13	$LaCl_3{\cdot}7H_2O$ (2 mol%)	3.5	35
14	$LaCl_3{\cdot}7H_2O$ (5 mol%)	3	62
15	$LaCl_3{\cdot}7H_2O$ (10 mol%)	3	83
16	$LaCl_3{\cdot}7H_2O$ (10 mol%)	3	81[b]
17	$LaCl_3{\cdot}7H_2O$ (15 mol%)	3	81

Conditions: ethyl acetoacetate (0.5 mmol), benzaldehyde (1 mmol), aniline (1 mmol) and 10 mol% catalyst in methanol (5 ml), stirring in room temperature

[a] Isolated yields

[b] Isolated yield when the reaction was carried out under reflux conditions

Table 3 $LaCl_3{\cdot}7H_2O$ (10 mol%) catalyzed one-pot synthesis of highly functionalized piperidines

Entry	R_1	R_2	R_3	**4**, **5**	Time (h)	Yield (%)[a]
1	H	H	Me	**4a**	3.5	80
2	2OMe	H	Me	**4b**	3.5	68
3	$3NO_2$	H	Me	**4c**	5	70
4	4CN	H	Me	**4d**	4.5	78
5	4Br	H	Me	**4e**	5	81
6	$4NO_2$	H	Me	**4f**	4.5	62
7	4Me	H	Me	**4g**	3.5	88
8	4MeO	H	Me	**4h**	4	84
9	H	4Cl	Me	**4i**	3.5	84
10	4F	4Cl	Me	**4j**	9	52
11	4Me	4Cl	Me	**4k**	3.5	79
12	H	H	Et	**5a**	3	83
13	2F	H	Et	**5b**	7.5	69
14	3F	H	Et	**5c**	3.5	73
15	3Br	H	Et	**5d**	5	70
16	$3NO_2$	H	Et	**5e**	5.5	49
17	3Me	H	Et	**5f**	4.5	66
18	4Me	H	Et	**5g**	4	69
19	4Et	H	Et	**5h**	4.5	67
20	4F	H	Et	**5i**	3.5	77
21	4Cl	H	Et	**5j**	3.5	82
22	H	4Cl	Et	**5k**	4	80
23	4Me	4Cl	Et	**5l**	3.5	73
24	4Et	4Cl	Et	**5m**	4.5	69
25	H	4Me	Et	**5n**	4.5	80
26	4Me	4Me	Et	**5o**	4	82
27	4Cl	4Me	Et	**5p**	5	77
28	4Me	$4NO_2$	Et	**5q**	8	74

Conditions: 1,3-dicarbonyl compound (0.5 mmol), aromatic aldehyde (1 mmol), aniline(1 mmol) and 10 mol% $LaCl_3{\cdot}7H_2O$ in 5 ml MeOH, stirring in room temperature

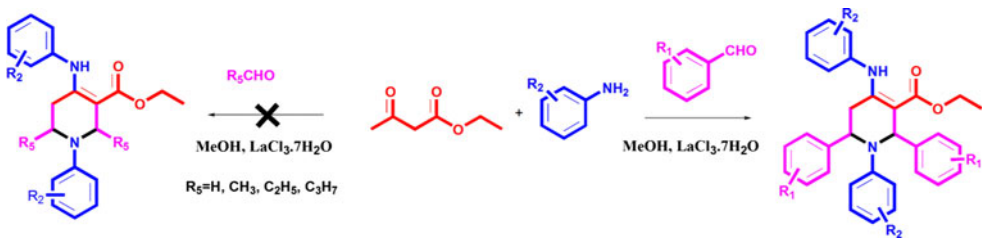
[a] Isolated yields

were allowed to react with ethyl acetoacetate under standard conditions affording substituted piperidine with good yields. Nitro group (at 3 and 4 positions) containing aldehyde gave moderate yields with both ethyl acetoacetate and methyl acetoacetate due to stable imine formation. Likewise a variety of aromatic anilines possessing electron withdrawing and electron donating groups, were allowed to react with ethyl acetoacetate and aromatic aldehydes under standard conditions and results are summarized in Table 3. Similarly for getting piperidine moiety, we treated ethyl acetoacetate and aniline with different aliphatic aldehydes including formaldehyde, acetaldehyde, and propanaldehyde under same reaction conditions. However, no desired compounds were formed in the reaction. This is due to the electron releasing nature of alkyl groups in aliphatic aldehydes. The reaction is shown in Scheme 1.

All the synthesized products were characterized by FTIR, H^1 NMR, C^{13} NMR and mass spectral analyses. The structures of **4a** and **5a** were determined by single crystal X-ray diffraction analysis shown in Fig. 1 and it can be concluded that the ring exists in trans form. The H^1 NMR spectral analyses of compounds **4a–4j** and **5a–5m** reveal that N–H peak comes around 10.250–10.350 ppm with the exception of **4b** which comes around 9.80 ppm. Proton present at the stereogenic center C-2 (denoted by asterisk in Scheme 2) position comes at around 6.35–6.55 ppm. Proton present at the stereogenic center is shifted towards the deshielding region, when the electron donating groups are present at para position on aromatic aldehyde ring. This is further confirmed by H^1 NMR spectra of compounds **5g–j.** In compound **5g** and **5h** stereogenic proton comes next to two aromatic protons but in the case of **5i** and **5j** stereogenic proton comes first followed by aromatic proton.

The possible reaction mechanism for this three-component reaction is described in Scheme 3. $LaCl_3{\cdot}7H_2O$ is Lewis acid, which serves as an acid catalyst for the construction of β-enaminone (**6**) formed by the reaction of ethyl acetoacetate with aniline and imine (**7**) which is formed in the reaction of benzaldehyde with aniline (Step 1). Benzaldehyde which is retained in the reaction mixture undergoes Knoevenagel condensation with β-enaminone leading to the formation of intermediate 8 and reactive form **8a** (Step 2). Due to the diene core present in intermediate **8a**, it proceeds towards an intramolecular aza Diels–Alder reaction with imine (serves as dienophile) which affords the expected piperidine (Step 3). Intermediates **6** and **7** had earlier been isolated from similar reaction.

Scheme 1 Reaction of 1,3-dicarbonyl compound, aniline with various aldehydes in the presence of $LaCl_3{\cdot}7H_2O$



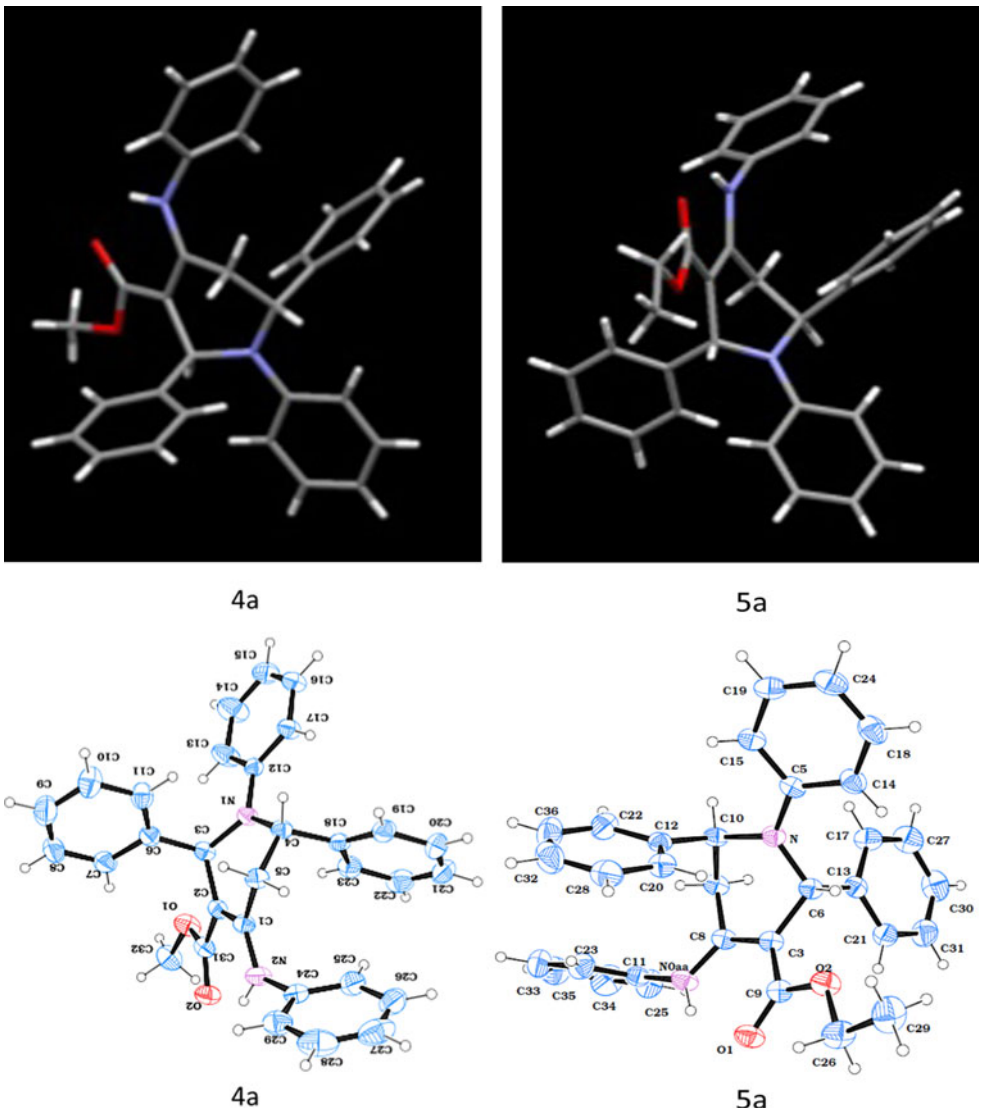
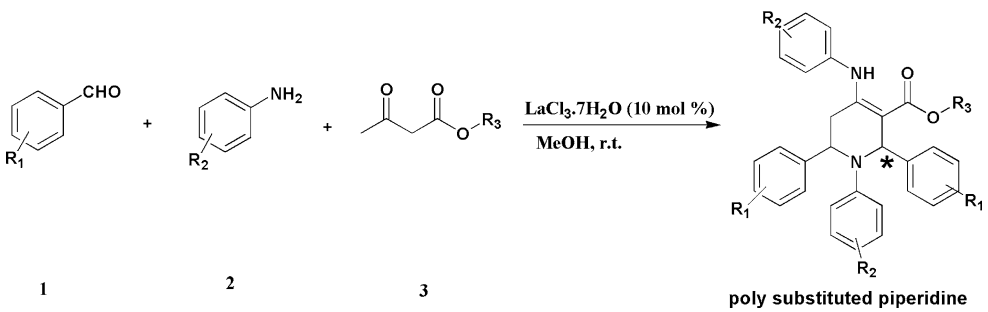


Fig. 1 Crystal structures of **4a** and **5a**



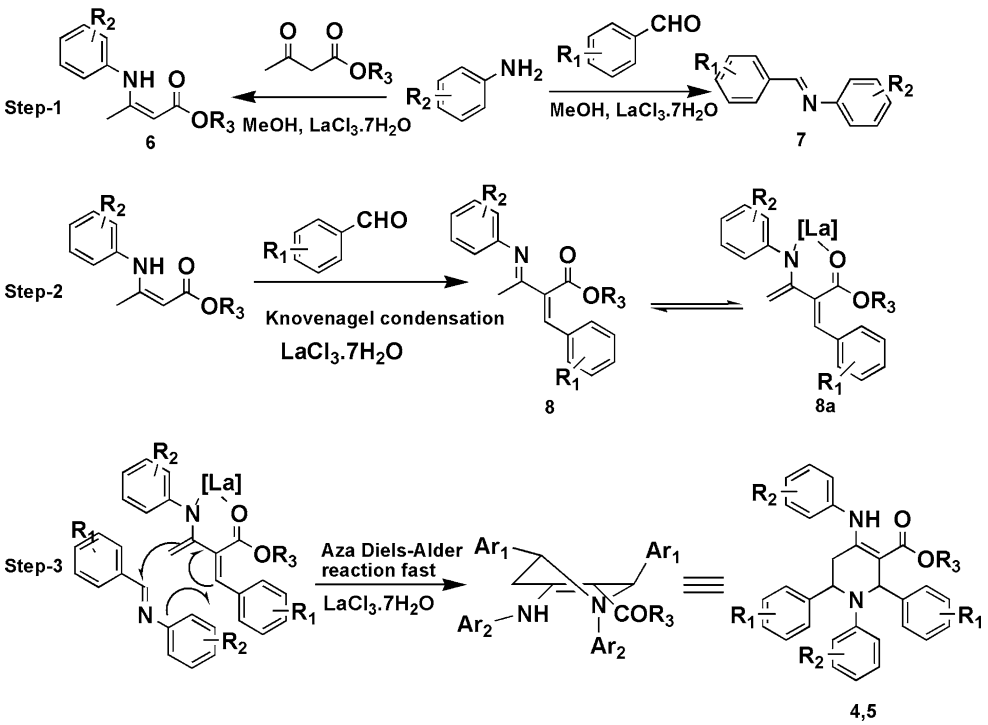
Scheme 2 Three-component one-pot reaction leading to poly substituted piperidines

3 Experimental Section

3.1 General Procedure for the preparation of Methyl 1,2,5,6-Tetrahydro-1,2,6-triphenyl-4-(phenylamino) pyridine-3-carboxylate (**4a**)

A mixture of β-keto ester (1 mmol), aniline (2 mmol) and $LaCl_3 \cdot 7H_2O$ (0.1 mmol) in 5 ml methanol was stirred at room temperature for 15 min followed by the addition of aldehyde (2 mmol) and stirring was continued for an appropriate time. The completion of the reaction was monitored by TLC. The solid product formed in reaction mixture was filtered, washed with methanol and recrystallized using ethanol and tetrahedrofuran (1:1 ratio). If the product was in gel form, it was purified by silica gel column chromatography using hexane and ethyl acetate as eluant.

Scheme 3 The possible mechanism for three-component one-pot reaction leading to poly substituted piperidine



White yellow solid; melting point: 192–194 °C: IR (KBr): 3250, 3024, 2949, 2867, 1815, 1661, 1606, 1504, 1449, 1375, 1321, 1245, 1183, 1070, 978, 920, 748, 646 cm^{-1}: H^1NMR (400 MHz, CDCl3)^{TM} ppm: 2.78–2.74 (d, $J = 14.8$ Hz, 1H), 2.89–2.84 (dd, $J = 30.4$, 5.6 Hz, 1H), 3.93 (s, 3H), 5.15(s, 1H), 6.29–6.26 (d, $J = 7.6$ Hz, 2H), 6.45 (s, 1H), 6.53–6.51 (d, $J = 8.4$ Hz, 2H), 6.61–6.58 (t, $J = 7.2$ Hz, 1H), 7.33–7.03 (m, 15H), 10.25 (br s, 1H, NH); C^{13}NMR (100 MHz, CDCl3)^{TM} ppm: 33.6, 51.0, 55.1, 58.2, 97.9, 112.9, 116.2, 125.8, 125.9, 126.4, 126.4, 126.6, 127.2, 128.3, 128.7, 128.9, 128.9, 137.8, 142.7, 143.9, 146.9, 156.3, 168.6;

4 Conclusion

In conclusion, we have developed a one-pot three-component intramolecular aza Diels–Alder reaction of aldehydes, aniline and 1,3-dicarbonyl compounds in the presence of 10 mol% of $LaCl_3 \cdot 7H_2O$ in MeOH as an efficient catalyst. The main feature of this strategy includes easy work up, mild reaction conditions, good yields and high atom economy. The current methodology is attractive for the preparation of a wide variety of biologically active highly functionalized piperidines.

Acknowledgments Umamahesh B and Sathesh V express their thanks to VIT management for providing financial support through research associateship. The authors express their gratitude to Dr. T. N. Guru Row, IISc, Bangalore and G. Sekar, IIT, Madras, India for crystal data.

References

1. Koukabi N, Kolvari E, Khazaei A, Zolfigol MA, Shaghasemic-Shaghasemi B, Khavasid HR (2011) Chem Commun 47:9230
2. Ghandi M, Jamea AH (2011) Tetrahedron Lett 52:4005
3. Wu H, Lin W, Wan Y, Xin H, Shi D, Shi Y, Yuan R, Bo R, Yin W (2010) J Comb Chem 12:31
4. Urushima T, Sakamoto D, Ishikawa H, Hayashi Y (2010) Org Lett 12:4588
5. Chen Y, Zhong C, Petersen JL, Akhmedov NG, Shi X (2009) Org Lett 11:2333
6. Xu J, Wei J, Bian L, Zhang J, Chen J, Deng H, Wu X, Zhang H, Cao W (2011) Chem Commun 47:3607
7. Jia XD, Wang XE, Yang CX, Huo CD, Wang WJ, Ren Y, Wang XC (2010) Org Lett 12:732
8. Barber DM, Sanganee H, Dixon DJ (2011) Chem Commun 47:4379
9. Watson PS, Jiang B, Scott B (2000) Org Lett 2:3679
10. Imamura S, Nishikawa Y, Ichikawa T, Hattori T, Matsushita Y, Hashiguchi S, Kanzaki N, Iizawa Y, Baba M, Sugihara Y (2005) Bioorg Med Chem 13:397
11. Weis R, Schweiger K, Faist J, Rajkovic E, Kungl AJ, Fabian WMF, Schunack W, Seebacher W (2008) Bioorg Med Chem 16:10326
12. Ishikawa M, Furuuchi T, Yamauchi M, Yokoyama F, Kakui N, Sato Y (2010) Bioorg Med Chem 18:5441
13. Zhang J, Zhang P, Liu X, Fang K, Lin G (2007) Bioorg Med Chem Lett 17:3769
14. Srinivas C, Kumar CNSP, Raju BC, Rao VJ, Naidu VGM, Ramakrishna S, Diwan PV (2009) Bioorg Med Chem Lett 19:5915
15. Davis FA, Chao B, Rao A (2001) Org Lett 3:3169
16. Arena G, Zill N, Salvadori J, Girard N, Mann A, Taddei M (2011) Org Lett 13:2294
17. Jarvis SBD, Charette AB (2011) Org Lett 13:3830
18. Ragoussi ME, Walker SM, Piccanello A, Kariuki BM, Horton PN, Spencer N, Snaith JS (2010) J Org Chem 75:7347
19. Sun J, Sun Y, Xia EY, Yan CG (2011) ACS Comb Sci 13:436

20. Sales M, Charette AB (2005) Org Lett 7:5773
21. Barluenga J, Mateos C, Aznar F, Valdes F (2002) Org Lett 4:3667
22. Ghorai MK, Halder S, Das RK (2010) J Org Chem 75:7061
23. Clarke PA, Zaytzev AV, Whitwood AC (2007) Tetrahedron Lett 48:5209
24. Khan AT, Parvin T, Choudhury LH (2008) J Org Chem 73:8398
25. Misra M, Pandey SK, Pandey VP, Pandey J, Tripathi R, Tripathi RP (2009) Bioorg Med Chem 17:625
26. Khan AT, Lal M, Khan MM (2010) Tetrahedron Lett 51:4419
27. Khan AT, Khan MM, Bannuru KKR (2010) Tetrahedron 66:7762
28. Wang HJ, Mo LP, Zhang ZH (2011) ACS Comb Sci 13:181
29. Mishra S, Ghosh R (2011) Tetrahedron Lett 52:2857
30. Mukhopadhyay C, Rana S, Butcher RJ, Schmiedekamp AM (2011) Tetrahedron Lett 52:5835
31. Verma S, Kumar S, Jain SL, Sain B (2011) Org Biomol Chem 9:6943
32. Ramachandran R, Jayanthi S, Jeong YT (2012) Tetrahedron 68:363
33. Pal S, Choudhury LH, Parvin T (2011) Mol divers. doi:10.1007/s11030-011-9339-9
34. Brahmachari G, Das S (2012) Tetrahedron Lett. doi:10.1016/j.tetlet.2012.01.042
35. Narasimhulu M, Reddy TS, Mahesh KC, Reddy SM, Reddy AV, Venkateswarlu Y (2007) J Mol Catal A 264:288
36. Kidwai M, Bhatnagar D (2010) Tetrahedron Lett 51:2700
37. Giuseppone N, Collin J (2001) Tetrahedron 57:8989
38. Moustafa MMAR, Pagenkopf BL (2010) Org Lett 12:4732
39. Lu J, Bai Y, Wang Z, Yang B, Ma H (2000) Tetrahedron Lett 41:9075