Tetrahedron Letters 56 (2015) 5920–5923

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Bipyridine carbaldehydes as electrophiles in the Morita–Baylis–Hillman reaction: synthesis of highly functionalized bipyridyl ligands and a macrocycle

Siddan Gouthaman, Somasundharam Periyaraja, Ponnusamy Shanmugam *

Organic Chemistry Division, Council of Scientific and Industrial Research (CSIR)-Central Leather Research Institute (CLRI), Adyar, Chennai 600020, India

ARTICLE INFO

Article history:
Received 12 August 2015
Revised 9 September 2015
Accepted 11 September 2015
Available online 11 September 2015

Keywords:
MBH reaction
Bipyridine
Electrophile
Pyridine-*N*-oxide
Spiro pyrrolidine oxindole

ABSTRACT

A simple and efficient Morita–Baylis–Hillman (MBH) reaction of bipyridine carbaldehydes and unexplored activated alkenes afforded highly functionalized bipyridyl ligands. Particularly, one-pot MBH reaction of 2,2′-bipyridine-4,4′-dicarbaldehyde and 2,2′-bipyridine-4-methyl-4′-carbaldehyde with 1,6-hexanediol diacrylate afforded a twenty membered bipyridyl macrocycle and bis MBH adducts, respectively. Synthetic transformations of mono and bis MBH adducts thus obtained have been demonstrated by preparing bipyridyl *N*-oxide and [3+2]-cycloadduct of azomethine ylide derived from isatin and proline.

© 2015 Elsevier Ltd. All rights reserved.

Introduction

Bipyridine[1] derivatives are key synthons in synthetic and material chemistry owing to their redox stability.[2] Bipyridyl based organometallics have led to various synthetic methods[3] as asymmetric catalysis.[4] Metal complexes with nitrogen ligands offer for the design of anticancer drugs,[5] tissue engineering[6] and in drug delivery.[7] In addition, oligopyridine-based heterocycles exhibit a high chemical stability, long-lived excited-state lifetime, reversible electrochemical behavior for their optoelectronic property.[8] Furthermore, these compounds have also shown potential applications in bio-sensing, assembly of catenanes and rotaxanes.[9] Bis arm pyridine receptors have been utilized for anion[10] and chiral molecular recognition.[11] Bipyridine based polymers could lead to the electrochromism and electroluminescent display devices.[12] Lack of general and efficient methods to manipulate bipyridine functionalization, most of the existing methods suffer arsenal strategies such as multi-step and stringent reaction conditions,[13] use of expensive and hazardous catalyst/reagents,[14] and prolonged reaction times are generally required.[15]

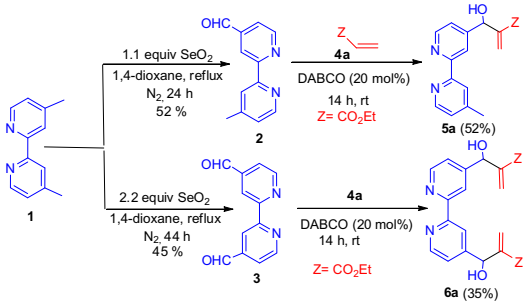
In view of the difficulty and importance for the functionalization of 2,2′-bipyridine, development of a simple, efficient, and expedient method for the functionalization of 2,2′-bipyridine is still in demand. The Morita–Baylis–Hillman (MBH) reaction[16] has been utilized as a synthetic tool in generating complex frameworks and has been used as building blocks in synthetic chemistry and bioactive molecules.[17] The versatility of the reaction has been demonstrated in the implementation of the MBH adducts.[18] We have studied the synthetic transformation of β-substituted MBH ester[19] derived from electrophiles such as aryl aldehydes, isatin, ferrocene carboxaldehyde, heteroaldehydes, and ninhydrin. However, to the best of our knowledge, there is no report on the synthesis of MBH adducts of 2,2′-bipyridine with unexplored Micheal acceptors, thus, functionalization of bipyridine via MBH reaction has been studied and the preliminary results are presented in this communication.

Initially, substrate 2,2′-bipyridine-4-methyl-4′-carbaldehyde **2** was prepared from 4,4′-dimethyl-2,2′-bipyridine **1** following a literature procedure,[20] while substrate 2,2′-bipyridine-4,4′-dicarbaldehyde **3**[21,22] was prepared from the treatment of compound **1** with 2.2 equiv of SeO_2 in 1,4-dioxane at reflux afforded dialdehyde **3** in 45% yield (Scheme 1). Significantly, the oxidation of **1** has been selectively achieved with SeO_2 which avoids the formation of corresponding bipyridine *N*-oxides.

Subsequently, MBH reaction of **2** with 1.2 equiv of classical activated alkene viz. ethyl acrylate **4a** and catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) under neat condition at rt for 14 h afforded the MBH adduct **5a** in 52% yield. On the other hand, under similar condition, MBH reaction of **3** with 2.3 equiv of **4a** provided bis MBH adduct **6a** in 35% yield (Scheme 1). Thus, to

* Corresponding author. Tel.: +91 44 24437130; fax: +91 44 24911589.
E-mail address: shanmu196@rediffmail.com (P. Shanmugam).

http://dx.doi.org/10.1016/j.tetlet.2015.09.032
0040-4039/© 2015 Elsevier Ltd. All rights reserved.



Scheme 1. Preparation of 2,2′-bipyridine-4-methyl-4′-carbaldehyde **2** and 2,2′-bipyridine-4,4′-dicarbaldehyde **3** and MBH reaction of **2** and **3** with ethyl acrylate **4a**.

obtain pure and optimum yield of MBH adducts **5a** and **6a**, optimization studies have been undertaken wherein mol % of catalyst, solvents, and reaction time are the variables considered. Thus, in THF as solvent, aldehydes **2** and **3** were found partially soluble with 20 mol % DABCO as catalyst, the reaction afforded MBH adducts **5a** and **6a** along with inseparable impurity (Table 1, entry 2) as evidenced from proton NMR spectrum. Use of methanol and 20 mol % DABCO, yielded products **5a** or **6a** with improved yields of 82% and 78%, respectively but still with impurities (Table 1, entry 3). Finally, among the various parameters tested (Table 1, entries 1–8), 10 mol % of DABCO in methanol for 10/12 h at rt was found to be an ideal condition for the MBH products **5a** and **6a** in 84% and 85% yields, respectively (Table 1, entry 7) without any impurity. Decreasing the time reduces the yields (Table 1, entry 8) and decreasing mol % of the catalyst took longer time for completion of the reaction (Table 1, entry 9). The structure of the mono MBH adduct **5a** and bis MBH adduct **6a** was assigned based on spectroscopic analysis such as FT-IR, ^{1}H NMR, ^{13}C NMR, DEPT-135, and mass spectrum.

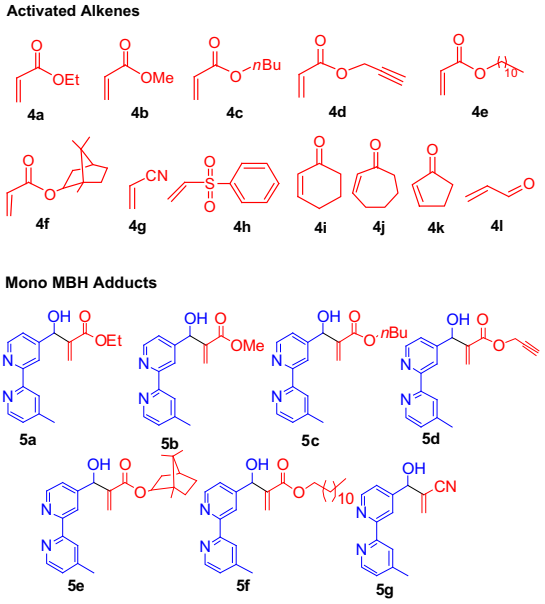
To demonstrate the scope and limitation of the MBH reaction of mono aldehyde **2**, various activated alkenes **4a–m** were used (Table 2). Thus, reaction of monoaldehyde **2** with unexplored acrylates **4a–f** and acrylonitrile **4g** afforded corresponding MBH adducts **5a–g** in very good yield (Table 2, entries 1–7). A little more time required for completing the reaction with lauryl acrylate **4e** and isobornyl acrylate **4f** (Table 2, entries 5 and 6). To our dismay, under optimized conditions, the reaction of bipyridine aldehyde **2** with activated alkenes **4h–l** failed to provide corresponding MBH adducts (Table 2, entries 8–12). Propargyl esters[23] are known as protecting group in organic synthesis. The reaction of unexplored

Table 1
Optimization of synthesis of MBH adducts **5a**/**6a**[a]

Entry	Substrate	Solvent	Time (h)	Catalyst (mol %)	Yield[b] (%)	
					5a	**6a**
1	2/3	Neat	14	20	52	35[c]
2	2/3	THF	14	20	65	54[d]
3	2/3	MeOH	14	20	82	78
4	2/3	Toluene	14	20	72	75[d]
5	2/3	DCM	14	20	65	60
6	2/3	MeOH	10/12	20	83	81
7	**2/3**	**MeOH**	**10/12**	**10**	**84**	**85**[e]
8	2/3	MeOH	7	10	70	60
9	2/3	MeOH	24/36	5	72	79

[a] Reactions were performed at rt, 1.1/2.2 equiv of **4a** was used for substrates **2** and **3**, respectively.
[b] Isolated yield.
[c] Performed without solvent and with 5% impurity.
[d] Aldehyde is partially soluble and afforded product along with 10% impurity.
[e] Optimized condition.

Table 2
Synthesis of MBH adducts **5a–g** of compound **2**

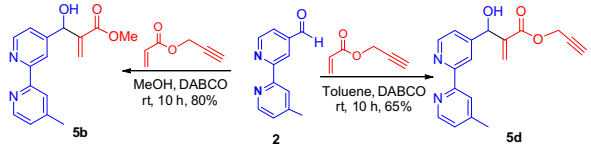


Entry	Activated alkene	Time (h)	Product[a,d]	Yield[b] (%)
1	**4a**	10	**5a**	83
2	**4b**	10	**5b**	80
3	**4c**	10	**5c**	83
4	**4d**	10.5	**5d**	65[c]
5	**4e**	13	**5e**	78
6	**4f**	12.4	**5f**	72
7	**4g**	13	**5g**	88
8	**4h**	14	—	—
9	**4i**	14	—	
10	**4j**	14	—	—
11	**4k**	14	—	—
12	**4l**	14	—	—

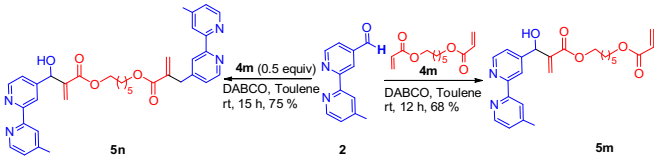
[a] Reactions were performed using 10% of DABCO in MeOH at rt.
[b] Isolated yield.
[c] Toluene at rt.
[d] Products were semisolid except **5g**.

activated alkene propargyl acrylate **4d** as Michael acceptor with bipyridine aldehyde **2** in methanol and a catalytic amount of DABCO, the propargyl group was found to be replaced by methanol to form MBH adduct **5b**. However, the reaction in toluene provided the desired MBH adduct **5d** in 65% yield (Scheme 2).

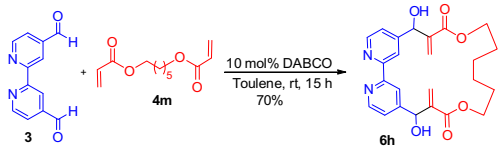
In order to diversify the synthesis and to understand the reactivity pattern, MBH reaction with an unexplored bis activated acrylate 1,6-hexanediol diacrylate (HDDA) **4m** has been probed for the first time. Thus, under optimized conditions 1.0 equiv of 2,2′-bipyridine-4-methyl-4′-carbaldehyde **2** with 1.3 equiv of **4m** proceeded smoothly to afford corresponding mono MBH adduct **5m** in 68% yield. Notably, when the reaction was carried out with 0.5 equiv of **4m** and 1.0 equiv of mono-aldehyde **2** at rt for 15 h it afforded two bipyridine entrapped bis MBH adduct **5n** in 75% yield (Scheme 3). Noteworthy that one-pot functionalization of bipyridine



Scheme 2. Synthesis of MBH adducts **5b** and **5d**.



Scheme 3. Synthesis of MBH adducts **5n** and **5m**.



Scheme 4. Synthesis of macrocyclic **6h**.

core and bis adduct **5n** formation and use of HDDA in MBH reaction is unknown.

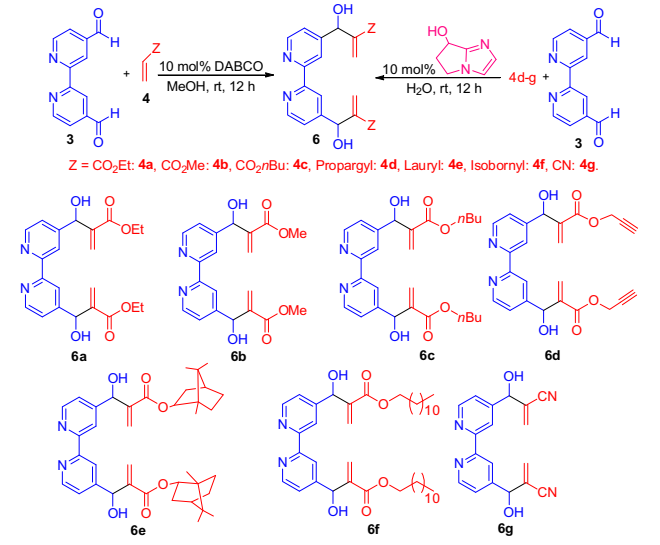
Simultaneous functionalization of both the rings of 2,2′-bipyridine is a difficult task in organic synthesis and for the development of bipyridine based materials. Thus, functionalization of 2,2′-bipyridine-4,4′-dicarbaldehyde **3** has been envisaged via MBH reaction with a number of Michael acceptors. The scope of this transformation was examined and found to be quite general with the acrylates **4a**–**f** and acrylonitrile **4g**, reacting smoothly to afford the respective bis MBH adducts **6a**–**6g** in good yield (Table 3, entries 1–7). Furthermore, MBH reaction of **3** with acrylates **4d**–**g** has been successfully performed in water as medium with 6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazol-7-ol as amine catalyst at rt to provide respective MBH adducts (Table 3, entries 8–11).

Significantly, we embarked a one-pot method where HDDA **4m** efficiently reacted with 2,2′-bipyridine-4,4′-dicarbaldehyde **3** in the presence of 10 mol % of DABCO to afford a macrocycle product **6h** in 70% yield (Scheme 4). This method allows for an instant and selective construction of macrocycle in a one pot, atom and step-economical manner from a relatively simple building block.

Having the MBH adducts **5** and **6** in hand, protection of –OH group with *p*-toluenesulfonyl chloride, *p*-toluenesulfonyl isocyanate, *p*-tolyl isocyanate, *p*-toluene isothiocyanate, di-*tert*-butyl dicarbonate, and acid halides was undertaken (Scheme 5). However, only RCOX was found to be reactive to provide compounds **11b**, and **12b** in 90% and 74% yields, respectively (Scheme 6). Furthermore, isomerization of MBH adducts **5** and **6** with nucleophile such as HX (X = Br, Cl, I), and $CH(OMe)_3$ and Montmorillonite K10 clay as solid acid catalyst under conventional or microwave irradiation condition failed to provide isomerized products. Upon isomerization with phenol/thiol nucleophiles, complex mixtures were formed (Scheme 5).

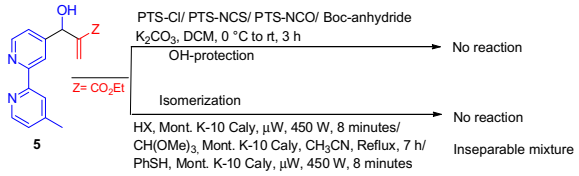
In order to demonstrate the synthetic transformation of MBH adducts **5b**/**6b**, reaction with 3 equiv of *m*-CPBA in DCM led to the formation of 2,2′-bipyridine-*N*-oxide derivatives **7b**/**8b** in 88% and 73% yields, respectively. Under the condition, with excess *m*-CPBA, no alkene epoxide formation was observed. Moreover, [3+2]-cycloaddition reaction of MBH adduct **5b**/**6b** was carried out with azomethine ylide generated in situ from isatin and proline in the presence of Mont. K10 clay afforded spiro pyrrolizidine

Table 3
Synthesis of bis MBH adducts **6a**–**6g** from **3**

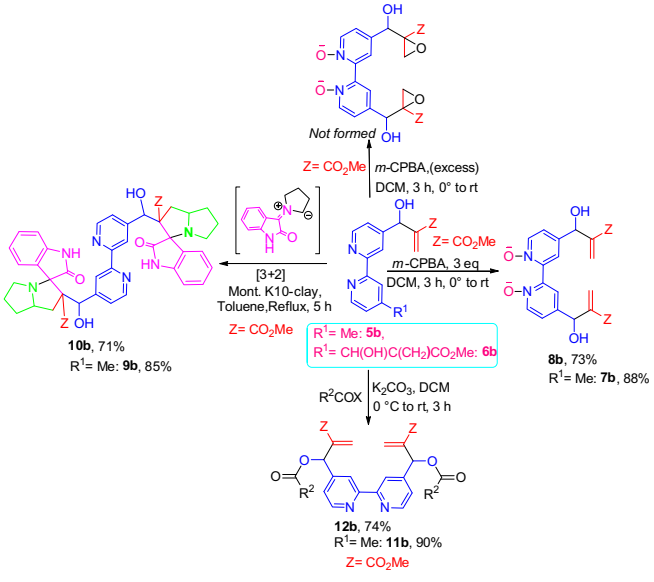


Entry	Activated alkene **4**	MBH adduct[a]	Time (h)	Yield of **6**[b] (%)
1	**4a**	**6a**	12	85
2	**4b**	**6b**	12	83
3	**4c**	**6c**	12	80
4	**4d**	**6d**	12	63
5	**4e**	**6e**	12	88
6	**4f**	**6f**	12	84
7	**4g**	**6g**	12	89
8	**4d**	**6d**	12	65[c]
9	**4e**	**6e**	12	89[c]
10	**4f**	**6f**	12	81[c]
11	**4g**	**6g**	12	87[c]

[a] All the reactions were performed at rt.
[b] Isolated yield after column purification.
[c] Reaction performed using 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-7-ol as catalyst in H_2O at rt.



Scheme 5. Attempted protection/isomerization of MBH adduct **5**.



Scheme 6. Synthetic transformation of MBH adducts **5** and **6**.

oxindoles **9b**/**10b** in 85% and 71% yields, respectively (Scheme 6). The structure of **7b**/**8b** and **9b**/**10b** was assigned based on spectroscopic data.

In conclusion, we have demonstrated unexplored Micheal acceptors for the synthesis of functionalized β-hydroxyl MBH ester appended bipyridine derivatives and a macrocycle. Simultaneous functionalization of both the rings of bipyridine has been achieved. The synthesized MBH adducts underwent protection, *N*-oxide formation and [3+2]-cycloaddition reactions resulting in structurally interesting bipyridine ligand derivatives. The synthetic potential opens a new pathway toward direct functionalization of the bipyridines as functional ligands. Further work on synthetic use of adducts is under investigation.

Acknowledgements

P.S. thanks the Director, CSIR-CLRI for infrastructure facilities. S. G. thanks CSIR (New Delhi) for the award of a Senior Research Fellowship. Financial support from the CSIR-12th five year plan project CSC-0201 is acknowledged. This manuscript has been assigned CSIR-CLRI communication number 3413.

Supplementary data

Supplementary data (detailed experimental procedure, characterization of the products and copies of spectra are provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.032.

References and notes

1. (a) Kaes, C.; Hosseini, M. W. *Chem. Rev.* **2000**, *100*, 3553–3590; (b) Newkome, G. R.; Patri, A. K.; Schubert, U. S. *Eur. J. Org. Chem.* **2004**, *234–235*.
2. (a) Hernandez, R.; Tseng, H.-R.; Zink, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 3370–3371; (b) Nguyen, T. D.; Stoddart, J. F.; Zink, J. I. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10029–10034.
3. (a) Kohara, J.; Yamamoto, T.; Yamamoto, A. *J. Organomet. Chem.* **1980**, *192*, 265–274; (b) Saito, T.; Uchida, Y.; Misono, A.; Yamamoto, A.; Morifuji, K.; Ikeda, S. *J. Am. Chem. Soc.* **1966**, *88*, 5198–5201.
4. (a) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, *1*, 1831–1842; (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497–526.
5. (a) Wilbuer, A.; Vlecken, D. H.; Meggers, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 3839–3842; (b) Geldmacher, Y.; Oleszak, M.; Sheldrick, W. S. *Inorg. Chim. Acta* **2012**, *393*, 84–102.
6. (a) Alavi, A.; Stupack, D. G. *Methods Enzymol.* **2007**, *426*, 85–101; (b) Malafaya, P. B.; Silva, G. A.; Reis, R. L. *Adv. Drug Delivery Rev.* **2007**, *59*, 207–233.
7. (a) Graf, N.; Lippard, S. J. *Adv. Drug Delivery Rev.* **2012**, *64*, 993–1004; (b) Rosler, A.; Vandermeulen, G. W. M.; Klok, H.-A. *Adv. Drug Delivery Rev.* **2001**, *53*, 95–108.
8. (a) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159–244; (b) Balzani, V.; Juris, A. *Coord. Chem. Rev.* **2001**, *211*, 97–115.
9. (a) Schmittel, M.; Kalsani, V. *Top. Curr. Chem.* **2005**, *245*, 1–53; (b) Zhou, M.; Bentley, D.; Ghosh, I. *J. Am. Chem. Soc.* **2004**, *126*, 734–735.
10. (a) Chellappan, K.; Singh, N. J.; Hwang, I. *Angew. Chem., Int. Ed.* **2005**, *117*, 2959–2963; (b) Verdejo, B.; Gil-Ramírez, G.; Ballester, P. *J. Am. Chem. Soc.* **2009**, *131*, 3178–3179.
11. (a) Borovinskaya, M. A.; Hau, C. W.; Cate, J. H. D. *Science* **2005**, *310*, 827–834; (b) Olenyuk, B.; Levin, M. D.; Whiteford, J. A.; Shield, J. E.; Stang, P. J. *J. Am. Chem. Soc.* **1999**, *121*, 10434–10435.
12. (a) Forrest, S. R.; Thompson, M. E. *Chem. Rev.* **2007**, *107*, 923–925; (b) Chen, S.; Deng, L.; Xie, J.; Peng, L.; Xie, L.; Fan, Q.; Huang, W. *Adv. Mater.* **2010**, *22*, 5227–5239.
13. Hunter, C. A.; Sanders, J. K. M.; Beddard, G. S.; Evans, S. *J. Chem. Soc., Chem. Commun.* **1989**. 1767–1767.
14. (a) Nelissen, H. F. M.; Schut, A. F. J.; Venema, F.; Feiters, M. C.; Nolte, R. J. M. *Chem. Commun.* **2000**, 577–578; (b) Ward, M. D. *Chem. Soc. Rev.* **1997**, *26*, 365–375.
15. (a) Komatsu, H.; Citterio, D.; Fujiwara, Y.; Minamihashi, K.; Araki, Y.; Hagiwara, M.; Suzuki, K. *Org. Lett.* **2005**, *7*, 2857; (b) Hunter, C. A.; Hyde, R. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1936–1939.
16. (a) Baylis, A. B.; Hillman, M. E. D. Offenlegungsschrift 2155113, US Patent 3,743,669, 1972 *Chem. Abstr.* **1972**, *77*, 34174;.; (b) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815; (c) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447–5674; (d) Batra, S.; Singh, V. *Tetrahedron* **2008**, *64*, 4511–4574; (e) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1–48; (f) Ma, G. N.; Jiang, J. J.; Shi, M.; Wei, Y. *Chem. Commun.* **2009**, 5496–5514.
17. (a) Nag, S.; Pathak, R.; Kumar, P. K.; Shukla, M.; Batra, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3824–3828; (b) Reddy, L. R.; Fournier, L. F.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2005**, *7*, 2699–2701; (c) Ciganek, E. In *Organic Reactions*; Paquette, L., Ed.; Wiley: New York, 1997; pp 201–350. Vol. 51.
18. (a) Krishna, P. R.; Kannan, V.; Reddy, P. V. N. *Adv. Synth. Catal.* **2004**, *346*, 603–606; (b) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533–2534.
19. (a) Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B.; Madhavan, S. *Tetrahedron Lett.* **2007**, *48*, 9190–9194; (b) Selvakumar, K.; Vaithiyanathan, V.; Shanmugam, P. *Chem. Commun.* **2010**, 2826–2828; (c) Solaiselvi, R.; Shanmugam, P. *Org. Lett.* **2013**, *15*, 5690–5693; (d) Viswambharan, B.; Selvakumar, K.; Madhavan, S.; Shanmugam, P. *Org. Lett.* **2010**, *12*, 2108–2111; (e) Madhavan, S.; Shanmugam, P. *Org. Lett.* **2011**, *13*, 1590–1593; (f) Malini, K.; Periyaraja, S.; Shanmugam, P. *Tetrahedron Lett.* **2015**, *56*, 5123–5127.
20. (a) Beer, P.; Szemes, F.; Passaniti, P.; Maestri, M. *Inorg. Chem.* **2004**, *43*, 3965–3975; (b) Salameh, A. S.; Ghaddar, T.; Isied, S. S. *J. Phys. Org. Chem.* **1999**, *12*, 247–254.
21. Della, C. L.; Dressick, J.; Von Zelewsky, A. J. *Heterocycl. Chem.* **1990**, *27*, 163–165.
22. Tak, J.; Kim, M.; Park, S.; Kim, B. H. *Monatshefte fuer Chem.* **2014**, *145*, 1101–1108.
23. Sridhar, P. R.; Chandrasekaran, S. *Org. Lett.* **2002**, *26*, 4731–4733.