Tetrahedron Letters 55 (2014) 1868–1872

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A rapid, highly efficient, and general protocol for the synthesis of functionalized triarylmethanes: a straightforward access for the synthesis of (−)-tatarinoid C

B. Madhu Babu, Pramod B. Thakur, N. Nageswara Rao, G. Santosh Kumar, H. M. Meshram *

Medicinal Chemistry and Pharmacology Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 7 October 2013
Revised 20 January 2014
Accepted 22 January 2014
Available online 31 January 2014

Keywords:
Triarylmethanes
Friedel–Crafts reaction
(−)-Tatarinoid C
$BF_3{\cdot}OEt_2$
Rapid synthesis

ABSTRACT

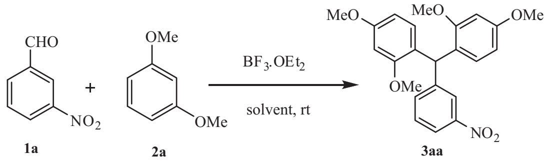
A rapid, efficient, and convenient synthesis of functionalized triarylmethane is described by the Friedel–Crafts alkylation of methoxybenzenes with a variety of aldehydes in the presence of $BF_3{\cdot}OEt_2$. The generality of the method is demonstrated by screening a variety of di- or tri-substituted arenes as well as substituted aromatic, heteroaromatic, and aliphatic aldehydes. (−)-Tatarinoid C is synthesized in a single step following the same protocol.

Triarylmethanes (TRAMs) are privileged structural motifs that are ubiquitous in dyes,[1] photo chromic agents,[2] and material sciences.[3] Some of the triarylmethane derivatives are found useful in medicinal and synthetic chemistry as protecting groups.[4] Additionally, substituted triarylmethanes are known to possess a wide range of biological activities such as antitumor,[5] antifungal,[6] anti-inflammatory,[6] antiviral,[7] antioxidant,[8] antitubercular,[9] as well as anti-diabetes.[10] TRAMs are also used as suitable building blocks for generating dendrimers and non linear optical chromophores.[11]

Due to such a prevalence and prominence of TRAMs, numerous methods have been reported for the synthesis of TRAMs. The classical approach for the synthesis of triarylmethane frameworks relies on Friedel–Crafts reactions of activated aromatics on aldehyde using various promoting systems.[12] These promoting systems mainly include various Lewis or Bronsted acids such as (a) iodine;[13a] (b) gold(III) chloride;[13b,13c] (c) silica gel-supported zinc bromide;[13d] (d) $B(C_6F_5)_3$;[13e] (e) $MeSO_3H$;[13f] (f) $[Ir(COD)Cl]_2$–$SnCl_4$;[6] (g) $Yb(OTf)_3$;[13g] (h) $FeCl_3$;[13h] (i) $H_3PW_{12}O_{40}$.[13i] Olah has reported the reaction of non-activated arenes and aldehydes in the presence of BF_3–H_2O.[14] Recently, Friedel–Crafts alkylation of 1,2,4-trimethoxybenzene with aldehydes or benzylic alcohols in the presence of trifluoromethanesulfonic acid afforded exclusively the corresponding triarylmethanes.[15] Though the reported methods are satisfactory, some of these methods often suffer from one or more drawbacks such as long reaction time,[13a] need of expensive toxic metals, harsh reaction conditions (e.g. high temperatures, pressure vessels),[13i,16] and poor yield of the desired product. In this context it is desirable to develop a convenient and rapid method for the synthesis of triarylmethanes.

Recently, $BF_3{\cdot}OEt_2$ has been used as Lewis acid for various organic transformations.[17] To the best of our knowledge there is no report on the direct synthesis of triarylmethanes by the reaction of substituted arenes with aldehyde using $BF_3{\cdot}OEt_2$ as a catalyst. Hence, as part of our[18] work in the development of useful methodology for the synthesis of biologically active molecules, herein we wish to report $BF_3{\cdot}OEt_2$ promoted rapid and efficient synthesis of new diversely functionalized triarylmethane scaffolds in very high yield under mild reaction conditions.

Initially, as a model reaction we attempted the reaction of 1,3-dimethoxybenzene (**2a**, 2 mmol) with 3-nitrobenzaldehyde (**1a**,



Scheme 1. Optimization of the reaction conditions.

---

* Corresponding author. Tel.: +91 40 27191643; fax: +91 40 27193275.
E-mail address: hmmeshram@yahoo.com (H.M. Meshram).

http://dx.doi.org/10.1016/j.tetlet.2014.01.107
0040-4039/

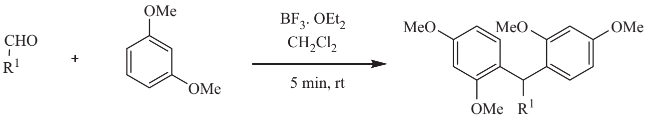
Table 1
Optimization of the reaction conditions[a]

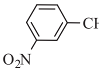
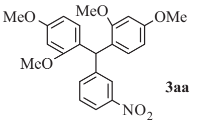
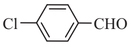
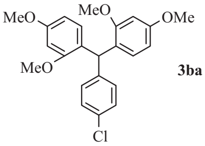
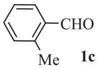
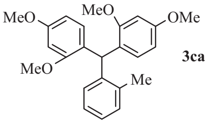
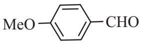
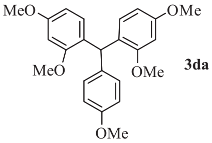
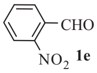
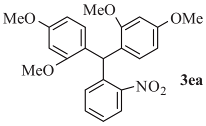
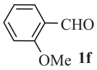
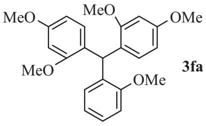
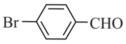
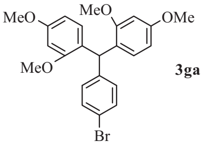
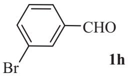
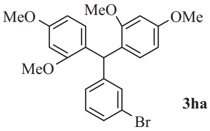
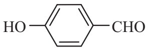
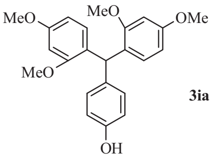
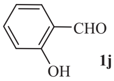
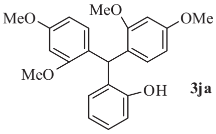
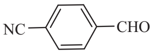
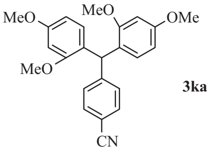
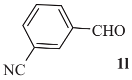
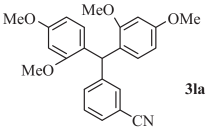
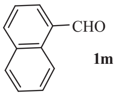
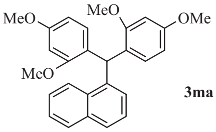
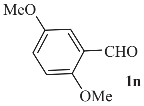
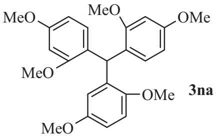
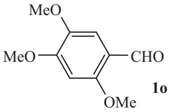
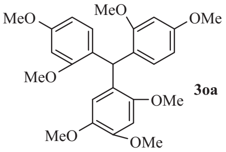
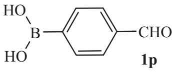
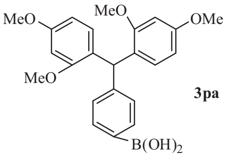
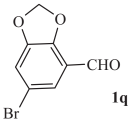
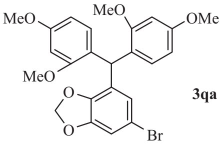
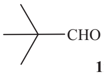
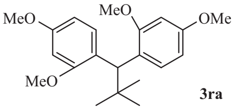
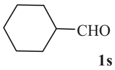
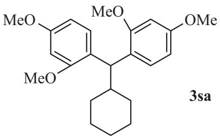
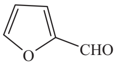
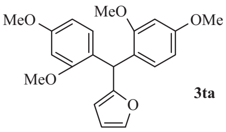
Entry	Catalyst (equiv)	Solvent	Time	Yield[b] (%)
1	$BF_3 \cdot OEt_2$ (0.01)	DCM	4 h	88
2	$BF_3 \cdot OEt_2$ (0.1)	DCM	10 min	90
3	$BF_3 \cdot OEt_2$ (1)	DCM	5 min	96
4	$BF_3 \cdot OEt_2$ (1.0)	DCM	5 min	78
5	$BF_3 \cdot OEt_2$ (1.0)	THF	5 min	52
6	$BF_3 \cdot OEt_2$ (1.0)	Toluene	5 min	23
7	$BF_3 \cdot OEt_2$ (0.0)	DCM	24 h	—

[a] All the reactions were conducted with 3-nitrobenzaldehyde **1a** (1 equiv); 1,3-dimethoxybenzene **2a** (2 equiv), in the presence of $BF_3 \cdot OEt_2$ in 2 mL solvent at room temperature.

[b] Isolated yield.

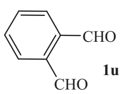
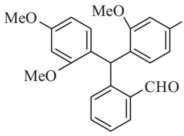
Table 2
Synthesis of new substituted triarylmethanes[a]



Entry	Aldehyde	Product	Yield[b] (%)
1	 **1a**	 **3aa**	96
2	 **1b**	 **3ba**	94
3	 **1c**	 **3ca**	93
4	 **1d**	 **3da**	95
5	 **1e**	 **3ea**	96
6	 **1f**	 **3fa**	92
7	 **1g**	 **3ga**	95
8	 **1h**	 **3ha**	95
9	 **1i**	 **3ia**	94
10	 **1j**	 **3ja**	93
11	 **1k**	 **3ka**	95
12	 **1l**	 **3la**	91
13	 **1m**	 **3ma**	92
14	 **1n**	 **3na**	93
15	 **1o**	 **3oa**	92
16	 **1p**	 **3pa**	91
17	 **1q**	 **3qa**	94
18	 **1r**	 **3ra**	94
19	 **1s**	 **3sa**	93
20	 **1t**	 **3ta**	94

(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehyde	Product	Yield[b] (%)
21	 **1u**	 **3ua**	93

[a] All products exhibited physical and spectral (NMR, Mass and IR) properties in accordance with the assigned structure.

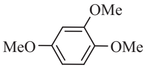
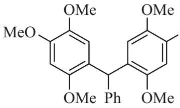
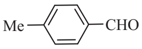
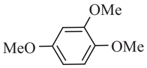
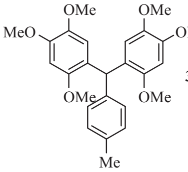
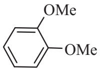
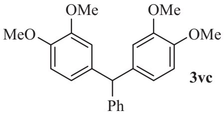
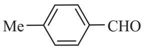
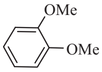
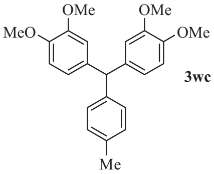
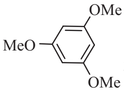
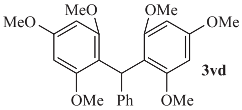
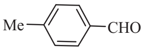
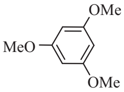
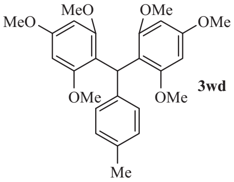
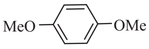
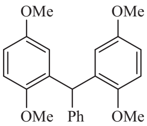
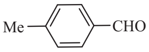
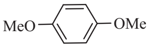
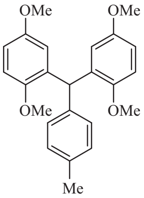
[b] Isolated yield.

1 mmol) in the presence of $BF_3{\cdot}OEt_2$ (1 equiv) in DCM at room temperature (Scheme 1). When we performed the reaction of 3-nitrobenzaldehyde and electron rich arene immediate color changes simply by mixing the reagent $BF_3{\cdot}OEt_2$ in the reaction mixture were observed. Fortunately, the reaction proceeded smoothly within 5 s at room temperature. After work-up triarylmethane (**3aa**) was isolated as a sole product which was confirmed by analyzing spectral data (Table 2, entry 1). The formation of the desired product was also confirmed by comparison with the spectral data for product obtained from one of the available literature procedures.[15] We screened various reaction conditions like reaction time, amount of $BF_3{\cdot}OEt_2$, and solvent nature (Table 1).

First we studied the different equivalents of $BF_3{\cdot}OEt_2$ and found that 1 equiv of $BF_3{\cdot}OEt_2$ was suitable for optimum conversion. The reaction with less equivalents of $BF_3{\cdot}OEt_2$ required longer reaction time for completion of the reaction (Table 1, entries 2 and 3).

The control reaction without $BF_3{\cdot}OEt_2$ was also performed, but the formation of the desired product **3aa** was not observed even

Table 3
Synthesis of substituted triarylmethanes[a]

Entry	Aldehyde	Arene	Product	Yield[b] (%)
1	Ph−CHO **1v**	 **2b**	 **3vb**	95
2	 **1w**	 **2b**	 **3wb**	96
3	Ph−CHO **1v**	 **2c**	 **3vc**	95
4	 **1w**	 **2c**	 **3wc**	95
5	Ph−CHO **1v**	 **2d**	 **3vd**	96
6	 **1w**	 **2d**	 **3wd**	94
7	Ph−CHO **1v**	 **2e**	 **3ve**	94
8	 **1w**	 **2e**	 **3we**	93

[a] All products exhibited physical and spectral (NMR, Mass and IR) properties in accordance with the assigned structure.

[b] Isolated yield.

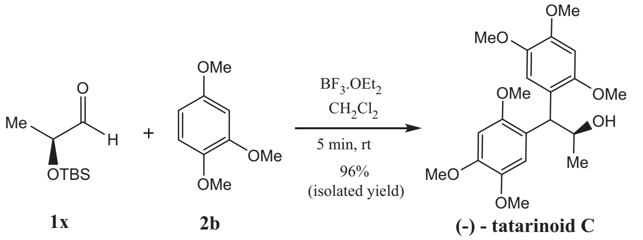
after stretching the reaction time up to 24 h (Table 1, entry 7). Next the effect of solvents was also tested by screening different solvents like DCE, THF, toluene, and DCM (Table 1, entries 3, 4, 5, and 6, respectively). The result demonstrated that DCM was a highly effective solvent in terms of reaction time and yield. It is worthy to mention that, the reaction worked very well in $BF_3\cdot OEt_2$ without using harsh reaction conditions and gave the corresponding TRAMs in a very high yield within very shorter reaction time at rt as compared to the previous methods.[14,15]

To determine the scope of this reaction, various methoxy benzenes and substituted aldehydes were examined under optimized conditions. We were delighted to find that the reaction of dimethoxybenzene and substituted aryl aldehydes resulted in high yield of product in very short time. There was no substantial effect of aryl aldehydes bearing electron withdrawing as well as electron donating substituents at various positions on the reaction (Table 2, entries 1–10, 14, and 15). The present reaction conditions tolerate various groups like nitrile, boronic acid for example 4-cyanobenzaldehyde and 4-formylphenylboronic acid reacted rapidly with 1,3-dimethoxybenzene to furnish high yield of corresponding triarylmethanes (Table 2, entries 11 and 16). Hindered aldehyde like naphthaldehyde also underwent smooth reaction with dimethoxybenzene and resulted in good yield of product (Table 2, entry 13).

The generality of this protocol was further strengthened by examining a variety of aldehydes. Furan-2-carboxaldehyde reacted with 1,3-dimethoxybenzene in standard conditions to afford desired TRAM in high yield (Table 2, entry 20). Similarly, 2,2-dimethylpropanal, 6-bromo-1,3-benzodioxole-4-carboxaldehyde, and cyclohexanecarboxaldehyde reacted analogously with dimethoxybenzene and resulted in triarylmethanes, respectively (Table 2, entries 17–19). The selectivity of the reaction was also established by screening dialdehydes like phthalaldehyde which afforded selectively the desired product **3ua** (Table 2, entry 21). The method is amenable for the synthesis of new compounds which are not prepared earlier. It is worthy to mention that the present method is relatively clean and isolation of product from reaction mixture is only by filter column.

To further extend the scope of the method we were keen to explore other substituted arenes in this reaction under the optimized reaction conditions. In this context we performed the reaction of other di-substituted arenes like 1,2-dimethoxybenzene and 1,4-dimethoxybenzene with different substituted aldehydes under standard reaction conditions and found the formation of desired products **3vc**, **3wc**, **3ve**, and **3we** (Table 3, entries 3, 4, 7, and 8). Similar results were obtained with tri-substituted arenes like 1,2,4-trimethoxybenzene (Table 3, entries 1 and 2) and 1,3,5-trimethoxybenzene (Table 3, entries 5 and 6). We presumed that $BF_3\cdot OEt_2$ promoted that present protocol may be a useful and alternate addition to the rapid and efficient synthesis of new diversely functionalized triarylmethane scaffolds in very high yield under mild reaction conditions.

The developed protocol was successfully applied to rapid and straightforward synthesis of phenylpropanoid natural product (−)-tatarinoid C.[19] When we treated chiral aldehydes **1x** prepared by reported method[20] with 1,2,4-trimethoxybenzene under optimized reaction conditions,[21] we directly obtained the (−)-tatarinoid C in very high yield within short reaction time (Scheme 2). It is important to note that, under our conditions, two processes Friedel–Crafts reactions and deprotection of the hydroxy group were taking place rapidly in one pot which resulted in the very high isolated yield of biologically important natural product (−)-tatarinoid C. The ^{1}H NMR and ^{13}C NMR spectral data of (−)-tatarinoid C were in good agreement with the data previously reported in the literature.[15]



Scheme 2. Rapid and efficient synthesis of (−)-tatarinoid C.

In conclusion, we have demonstrated operationally simple, highly efficient, and rapid protocol for the synthesis of diversely functionalized triarylmethane scaffolds by the Friedel–Crafts alkylation of substituted benzenes with aldehydes in the presence of $BF_3\cdot OEt_2$. Moreover, the developed method is general and applicable for variety of aldehydes and arenes. The discovery and development of this protocol led to the rapid and straightforward access to biologically important phenylpropanoid natural product (−)-tatarinoid C. This method ought to be of great value as a mild, rapid, efficient, and a general procedure for the synthesis of diversely functionalized triarylmethanes from readily available starting materials. Further studies on the application of this methodology for the synthesis of biologically important natural products is currently ongoing in our laboratory and results will be published elsewhere in due course.

Acknowledgments

The authors B.M.B., P.B.T., N.N.R., and G.S.K. thank CSIR-UGC for the award of a fellowship and to Dr. Ahmed Kamal, Outstanding Scientist and Head, MCP Division, IICT, for his support and encouragement.

The authors thank CSIR, New Delhi for financial support as part of XII Five Year plan programme under title ORIGIN (CSC-0108).

References and notes

1. (a) Lewis, E. S.; Perry, J. M.; Grinstein, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 899; (b) Duxbury, D. F. *Chem. Rev.* **1993**, *93*, 381; (c) Guinot, S. G. R.; Hepworth, J. D.; Wainwright, M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 297; (d) Rys, P.; Zollinger, H. *Fundamentals of the Chemistry and Application of Dyes*; Wiley-Interscience: NewYork, NY, 1972; (e) Muthyala, R. Chemistry and Applications of Leuco Dyes In Katrizky, A. R., Sabongi, G. J., Eds.; Plenum: New York, NY, 1997.
2. Irie, M. *J. Am. Chem. Soc.* **1983**, *105*, 2078.
3. (a) Das, S. K.; Shagufta; Panda, G. *Tetrahedron Lett.* **2005**, *46*, 3097; (b) Noack, A.; Hartmann, H. *Chem. Lett.* **2002**, 644; (c) Meier, H.; Kim, S. *Eur. J. Org. Chem.* **2001**, 1163; (d) Brasselet, S.; Cherioux, F.; Audebert, P.; Zyss, J. *Chem. Mater.* **1999**, *11*, 1915.
4. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, NY, 1999.
5. Lewis, M. R.; Goland, P. P. *Cancer Res.* **1952**, *12*, 130.
6. Podder, S.; Choudhury, J.; Roy, U. K.; Roy, S. *J. Org. Chem.* **2007**, *72*, 3100.
7. (a) Mibu, N.; Yokomizo, K.; Uyeda, M.; Sumoto, K. *Chem. Pharm. Bull.* **2005**, *53*, 1171; (b) Mibu, N.; Yokomizo, K.; Uyeda, M.; Sumoto, K. *Chem. Pharm. Bull.* **2003**, *51*, 1325.
8. Mibu, N.; Sumoto, K. *Chem. Pharm. Bull.* **2000**, *48*, 1810.
9. (a) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289; (b) Panda, G.; Shagufta; Mishra, J. K.; Chaturvedi, V.; Srivastava, A. K.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem.* **2004**, *12*, 5269.
10. Ellsworth, B. A.; Ewing, W. R.; Jurica, E.; U.S. Patent Application 2011/0082165A1, Apr 7 **2011**.
11. (a) Baker, L. A.; Sun, L.; Crooks, R. M. *Bull. Korean Chem. Soc.* **2002**, *23*, 647; (b) Sanguinet, L.; Twieg, R. J.; Wiggers, G.; Mao, G.; Singer, K. D.; Petschek, R. G. *Tetrahedron Lett.* **2005**, *46*, 5121.
12. (a) Nair, V.; Thomas, S.; Mathew, S. C.; Abhilash, K. G. *Tetrahedron* **2006**, *62*, 6731; (b) Schick, J. W.; Crowley, D. J. *J. Am. Chem. Soc.* **1951**, *73*, 1377; (c) Ungnade, H. E.; Crandall, E. W. *J. Am. Chem. Soc.* **1949**, *71*, 2209; (d) Pratt, E. F.; Green, L. Q. *J. Am. Chem. Soc.* **1953**, *75*, 275.
13. (a) Jaratjaroonphong, J.; Sathalalai, S.; Techasauvapak, P.; Reutrakul, V. *Tetrahedron Lett.* **2009**, *50*, 6012; (b) Nair, V.; Abhilash, K. G.; Vidya, N. *Org. Lett.* **2005**, *26*, 5857; (c) Nair, V.; Vidya, N.; Abhilash, K. G. *Synthesis* **2006**, *21*, 3647; (d) Kodomari, M.; Nagamatsu, M.; Akaike, M.; Aoyama, T. *Tetrahedron Lett.* **2008**, *49*, 2537; (e) Chandrasekhar, S.; Khatun, S.; Rajesh, G.; Raji Reddy, Ch. *Tetrahedron Lett.* **2009**, *50*, 6693; (f) Cook, M. P.; Ando, S.; Koide, K.

Tetrahedron Lett. **2012**, *53*, 5284; (g) Genovese, S.; Epifano, F.; Caroline, P.; Curini, M. *Eur. J. Org. Chem.* **2009**, *8*, 1132; (h) Li, Z.; Duan, Z.; Kang, J.; Wang, H.; Yu, L.; Wu, Y. *Tetrahedron* **2008**, *64*, 1924; (i) Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Mohammadiannejad-Abbasabadi, K.; Khavasi, H. R. *Eur. J. Org. Chem.* **2011**, *7*, 1357.

14. Prakash, G. K. S.; Panja, C.; Shakhmin, A.; Shah, E.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2009**, *74*, 8659.
15. Wilsdorf, M.; Leichnitz, D.; Reissig, H.-U. *Org. Lett.* **2013**, *15*, 2494.
16. (a) Raid, A.; Mouloungui, Z.; Delmas, M.; Gaset, A. *Synth. Commun.* **1989**, *19*, 3169; (b) Muthyala, R. *Dyes Pigments* **1994**, *25*, 303; (c) Katritzky, A. R.; Toader, D. *J. Org. Chem.* **1997**, *62*, 4137.
17. (a) Heaney, H. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, Vol. 1, pp 651–664, and references therein; (b) McKay, W. R.; Proctor, G. R. *J. Chem. Soc., Perkin Trans.* **1981**, *1*, 2435; (c) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108; (d) Maruyama, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8068; (e) Aubrecht, K. B.; Winemiller, M. D.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 11084; (f) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275; (g) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46; (h) Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 5451; (i) Jaric, M.; Haag, B. A.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2011**, *13*, 2306; (j) Fujita, M.; Yoshida, Y.; Miyata, K.; Wakisaka, A.; Sugimura, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7068; (k) Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301; (l) Faggi, E.; Sebastian, R. M.; Pleixats, R.; Vallribera, A.; Shafir, A.; Rodriguez-Gimeno, A.; Ramirez de Arellano, C. *J. Am. Chem. Soc.* **2010**, *132*, 17980; (m) Dohi, T.; Morimoto, K.; Takenaga, N.; Goto, A.; Maruyama, A.; Kiyono, Y.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 109; (n) Shi, L.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 6939; (o) Takada, T.; Arisawa, M.; Gyoten, H.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698; (p) Lei, W.; Min, S. *Tetrahedron* **2011**, *67*, 5732; (q) Ningning, W.; Shuying, C.; Chao, Z.; Ping, L.; Yanguang, W. *Tetrahedron* **2013**, *69*, 647; (r) Robyn, A. B.; William, W. O. *Tetrahedron* **2013**, *69*, 1539; (s) Guangwei, Y.; Yuanxun, Z.; Ningning, W.; Ping, L.; Yanguang, W. *Tetrahedron* **2013**, *69*, 835; (t) Madabhushi, S.; Chinthala, N.; Jillella, R.; Godala, K. R.; Mallu, K. R.; Beeram, C. R. *Tetrahedron Lett.* **2011**, *52*, 4701; (u) Kai, L.; Jiangmin, C.; Jeremy, C.; Shijun, Z. *Tetrahedron Lett.* **2013**, *54*, 2070; (v) Srinu, G.; Srihari, P. *Tetrahedron Lett.* **2013**, *54*, 2382; (w) Yadaganahalli, K. B.; Gejjalagere, S. L.; Saji, T.; Koravangala, S. V. K.; Challanayakanahally, S. P. K.; Kanchugarakoppal, S. R.; Marilinganadoddi, P. S. *Tetrahedron Lett.* **2013**, *54*, 2693; (x) Nicholas, G. M.; Andrew, M. H. *Tetrahedron Lett.* **2013**, *54*, 2960; (y) Lee, W.; Jung, J.-W.; Jang, J.; Yun, H.; Suh, Y.-G. *Tetrahedron Lett.* **2013**, *54*, 5167; (z) Quan, C.; Xavier, M. J.; Paul, K. *J. Am. Chem. Soc.* **2013**, *135*, 4958.
18. Meshram, H. M.; Thakur, P. B.; Babu, B. M.; Bangade, V. M. *Tetrahedron Lett.* **2012**, *53*, 1780.
19. Ganjewala, D.; Srivastava, A. K. *Asian J. Plant Sci.* **2011**, *10*, 182.
20. Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180.