Green Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. P. Parvathaneni, B. raktani and J. vaidya, *Green Chem.*, 2017, DOI: 10.1039/C7GC01483J.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/green-chem

View Article Online
DOI: 10.1039/C7GC01483J

Journal Name

COMMUNICATION

An Eco-Economical Protocol for Direct Conversion of Baylis Hillman Alcohols to β-Chloro Aldehydes in water

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Raktani Bikshapathi, Sai Prathima Parvathaneni*and Vaidya Jayathirtha Rao*

Abstract: This paper describes an atom-economical strategy for the direct conversion of Baylis Hillman Alcohols to β-chloro aldehydes under metal free conditions with excellent functional group tolerance. The use of stable-nontoxic oxone as terminal oxidant along with an inexpensive salt (sodium chloride) as halogen source and water as the reaction medium makes this chemical synthetic process more viable and environmentally benign contributing towards green chemistry.

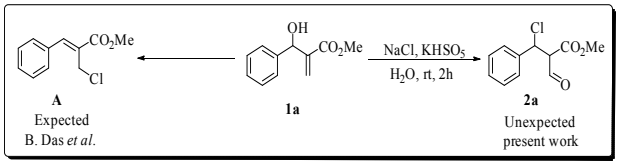
Introduction

Halogenated carbonyl compounds are versatile synthons to generate more complex organic architectures and multitude of heterocyclic compounds.[1] The most expedient methods for the synthesis of β-halo carbonyl compounds are conjugate addition of a hydrogen halide to an enone and the electrophilic addition of an acyl chloride to an olefin. They serve as reactive intermediates for late-stage function alization of pharmaceutically important drugs.[2] Traditional methods for electrophilic chlorination usually involve the use of molecular chlorine with a metal catalyst under relatively harsh conditions.[3] Significant progress was achieved to replace environmentally hazardous molecular chlorine through alternative N-chlorosuccinimide (NCS) for electrophilic chlorination in organic synthesis.[4] In terms of green chemistry perspective several environmentally benign protocols involving direct oxidative chlorination with chloride anions (HCl, KCl, NaCl etc.) in the presence of an oxidant has been developed to access halogenated carbonyl compounds and to surpass the existing literature.[5] Oxone is an effective oxidizing agent with a large scope of synthetic applications.[6] Over the years, oxone has become a versatile reagent in terms of its stability, solubility (water soluble nature), manipulative simplicity and that of being non-toxic and cost-effective reagent.[7]

The Morita-Baylis–Hillman (MBH) adducts are densely functionalized molecules which are generally used as advanced synthetic intermediates for construction of a plethora of natural products, and drug molecules.[8] In general, β-halo carbonyl compounds can be synthesized via halogenation of the corresponding carbonyls or oxidation and subsequent β-halogenation of alcohols in a two-step sequence.[9] In terms of economy, one-pot oxidation with subsequent halogenation would be more appropriate. In this scenario, the conversion of alcohols to the corresponding α-chloro carbonyl derivatives has been reported using trichloroisocyanuric acid (TCCA)[10]. In the literature, very few reports exists for preparation of β-halo aldehydes compared to ketones as they are proved to be unstable.[11]

Oxone and sodium chloride supported on wet alumina have been reported for the preparation of N-chloroamides.[12] To the best of our knowledge, the use of a stoichiometric amount of oxone together with NaCl has been explored for the first time for MBH derived alcohols. In an attempt to develop sustainable chemical process,[13] we have built up an efficient protocol by employing NaCl/Oxone[14] that's largely suitable for an aqueous system. Apart from bringing experimental simplicity and efficiency, this method significantly eliminates the organic wastes from solvents/reagents.

As part of the continuing efforts in our laboratory toward the development of metal-free oxidative transformations,[15] we have focused on realizing the synthetic potential of MBH



Scheme 1 One-pot synthesis of β-Chloro Aldehydes

Crop Protection Chemicals, Organic Division II,
Indian Institute of Chemical Technology, Uppal Road Tarnaka,
Hyderabad-500 607, India. Fax: (+)91 40 27193382; Tel: (+) 91 40 27193933;
e-mail: saiprathimaiict@gmail.com; vaidya.opv@gmail.com

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

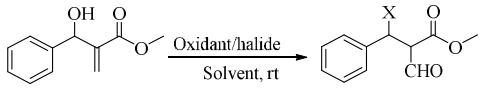
View Article Online
DOI: 10.1039/C7GC01483J

chemistry.[15c] To our surprise the reaction of **1a** with aqueous NaCl/Oxone was finished in 2 hour, thus affording an unexpected product **2a** with 100% conversion than the expected Das et al. accomplished product **A** as represented in Scheme 1.[16] These results inspired us to examine the reaction of the MBH alcohol **1a** with NaCl and oxone at room temperature in water.

Herein we report one-pot synthesis of β-chloro aldehydes from MBH adducts using sodium chloride as chloro source and oxone (potassium monopersulfate) as an oxidant. This process not only represents a novel cascade transformation but provides direct access to potential β-chloro aldehydes in good to excellent yields with high selectivity.

Results and discussion

Table 1 Optimization of reaction conditions[a]



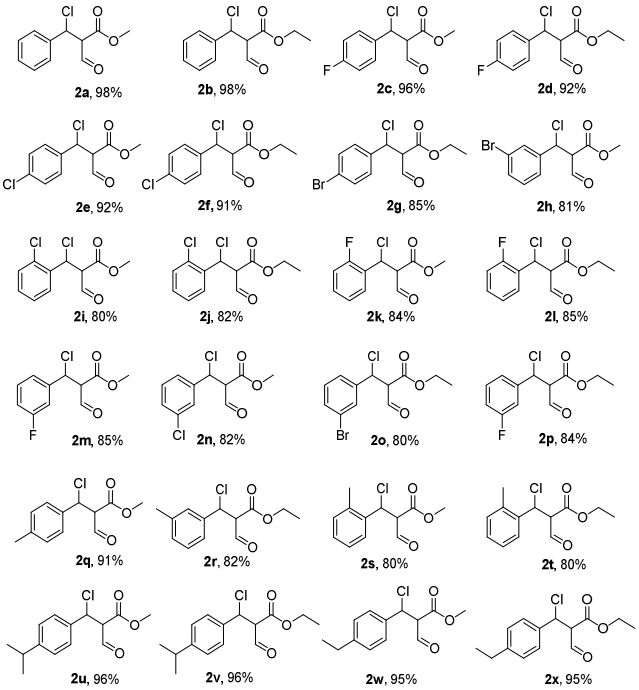
1a **2a, X = Cl** **3a, X = Br**

Entry	Oxidant (equiv)	Halide source (equiv)	Solvent	Yield[b] (%)
1	Oxone (1.2)	NaCl (4.0)	CH_3CN	95 **(2a)**
2	Oxone (1.2)	NaCl (2.0)	CH_3CN	75 **(2a)**
3	Oxone (1.2)	NaCl (2.0)	DCM	60 **(2a)**
4	Oxone (1.2)	NaCl (2.0)	DCE	80 **(2a)**
5	Oxone (1.2)	NaCl (2.0)	DMF	60 **(2a)**
6	Oxone (1.2)	NaCl (2.0)	H_2O	98 **(2a)**
7	Oxone (1.0)	NaCl (1.0)	H_2O	80 **(2a)**
8	Oxone (1.2)	NaCl (1.0)	H_2O:MeOH	85 **(2a)**
9	Oxone (1.2)	NaCl (1.0)	H_2O:CH_3CN	80 **(2a)**
10	Oxone (1.2)	NaCl (1.0)	H_2O:THF	60 **(2a)**
11	Oxone (1.2)	NaCl (1.0)	H_2O:1,4 dioxane	65 **(2a)**
12	Oxone (1.2)	NaBr (2.0)	H_2O:CH_3CN	20 **(3a)**
13	Oxone (1.2)	KBr (2.0)	H_2O:CH_3CN	30 **(3a)**
14	Oxone (1.2)	LiBr (2.0)	H_2O:CH_3CN	–
15	–	NaCl (2.0)	H_2O	–
16	Oxone (1.2)	–	CH_3CN	–

[a]Reaction conditions: Substrate **1a** (1.0 equiv) in H_2O (2 mL) for 2 h at room temperature. [b]Isolated yields.

In accordance with MBH oxidation reports,[14a] our research laboratory has focused on investigating oxone for selective oxidations. The Morita–Baylis–Hillman (MBH) alcohol **1a** were chosen as the model substrate for selective oxidation with oxone (1.2 equiv) and NaCl (4 equiv) as chlorine source in acetonitrile system (Table 1, entry 1). To our surprise, we have found unexpected **2a** as the sole product with 95% yield. Even though amount of halide source was decreased to 2 equiv, the reaction resulted in 80% of the functionalized product (entry 4) in DCE compared to other solvents (entries 2, 3 & 5). As our laboratory is involved in on-water catalysis[12] we have performed the reaction in water by employing NaCl (2 equiv) and oxone (1.2 equiv) and observed increase in the product yield (entry 6). Notably there was decline in the yield of the product with decrease in amounts of both NaCl and oxone (entry 7). The addition of water improved both the conversion and the reaction yield (entry 6). Furthermore the combination of water with (1:1) mixture of organic solvents with 1 equiv of halide source didn't have considerable effect on the product yields (entries 8-11). We have observed NaBr and KBr as halo source were ineffective in affording the desired bromo product **3a** in low yields (entry 12 & 13). Whereas LiBr is not suitable for this system (entry 14). The reaction did not proceed in absence of oxone as well as NaCl indicating the combination in aqueous phase is required for the generation of the desired product **2a** (entry 15 and 16).

Table 2 Substrate scope for MBH functionalization[a,b]



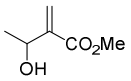
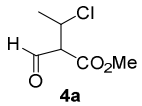
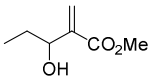
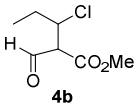
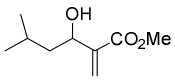
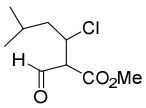
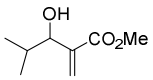
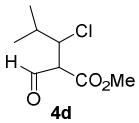
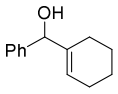
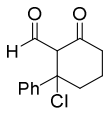
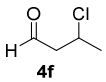
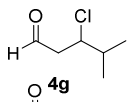
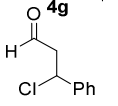
[a]All the reactions were carried out in the presence of 1.0 equiv of **1**, 1.2 equiv of oxone, 2 equiv of NaCl, in 2 mL of H_2O at room temperature for 2h. [b]Isolated yields.

To investigate the generality of the oxidation of MBH alcohols with oxone, various structurally diverse alcohols were prepared from acrylates and were tested as substrates under optimized conditions. All the MBH adducts (**1a–1x**) gave corresponding β-chloro aldehyde derivatives (**2a–2x**) with good to excellent yields (Table 2). The reactions with different electron-donating and electron-withdrawing

View Article Online
DOI: 10.1039/C7GC01483J

substituents on the aryl ring of the MBH alcohols were tolerated leading to high yields of the selective oxidized products. The use of MBH alcohol **1a** as model substrate proved to be effective in the formation of aldehyde **2a** in 98% yield. There is no change in the reaction yields for ethyl acrylate derived MBH alcohol in producing the corresponding aldehyde **2b**. Substrates bearing electron-withdrawing substituent (F, Cl and Br) at *para* position were successfully oxidised to produce the corresponding products **2c** (96%) **2d** (92%) **2e** (92%) **2f** (91%) and **2g** (85%) respectively. In case of *ortho* and *meta* halo substituted at phenyl ring also underwent the reaction smoothly to give the corresponding products (**2h-2p**) in low yields (80-84%) when compared to *para* substituted MBH alcohols. However electron-donating substituted MBH adducts also gave good yields (**2q-2x**). The more sterically hindered *para isopropyl*-substituted substrates was transformed into **2u** and **2v** (96%) at high yields.

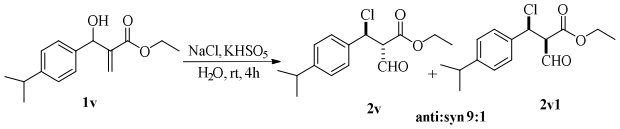
Table 3 Substrate scope for allylic alcohol functionalization[a,b]

Entry	Substrate	Product	Yield (%)[b]
1		 **4a**	–
2		 **4b**	–
3		 **4c**	–
4		 **4d**	–
5		 **4e**	82
6		 **4f**	–
7		 **4g**	–
8		 **4h**	quan[c]

[a]Reaction conditions: Substrate (1.0 equiv) in H_2O (2 mL) for 2 h at room temperature. [b]Isolated yields. [c]Quantative Yield analysed by Crude NMR.

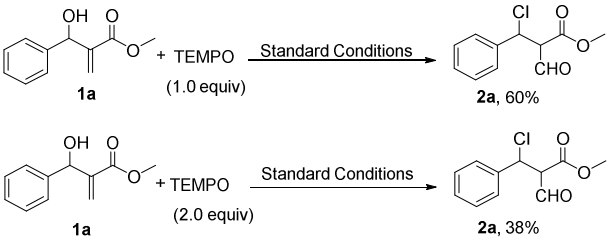
In addition we have extended the scope of the developed protocol to MBH adducts derived from aliphatic aldehydes to accomplish valuable β-chloro aldehyde products (Table 3). However this method was ineffective for aliphatic substrates, as alkyl migration was not observed to provide desired products **4a**, **4b**, **4c** and **4d** (Table 3, entries 1-4). To understand the feasibility of the reaction without ester group we have performed with aliphatic allylic alcohols and desired product was not formed (Table 3, entries 6 & 7). Pleasingly, under the optimized conditions cyclohexenone derived MBH adduct gave good yield (82%) of the desired product **4e** (Table 3, entry 5). A similar result was achieved with 1-phenylprop-2-en-1-ol substrate affording the product **4h** (Table 3, entry 8).

We then studied the selectivity of oxidative chlorination with NaCl/Oxone system in which the *anti*-isomer **2v** predominated over the *syn*-isomer **2v'**[1] by upto 9:1 was observed from NMR spectra analysis of the crude product as shown in scheme 2 (see supporting information).



Scheme 2. Oxidative chlorination of **1v**

In order to expand insights into the reaction mechanism of this oxidative transformation, a control experiment was carried out by using radical-trapping reagent 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO). This showed the variation in the reaction yield of the desired product **2a** (scheme 3). These results indicated that the present reaction may not proceed via a radical pathway.



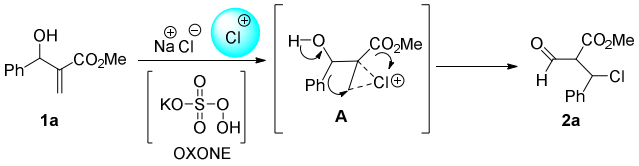
Scheme 3. Control Experiment

We have proposed a possible reaction pathway for the oxidation of MBH alcohols with oxone as represented in Scheme 4. In general allylic alcohols and their derivatives undergo semipinacol rearrangement to give synthetically useful β-halo carbonyl compounds induced by highly electrophilic Halonium ions.[17] Generally, electrophiles such as halogeniums, can be generated by addition of C=C bond and initiate rearrangements.[18] The umpouling-based oxidative transformation of halides into halonium ions takes place in presence of oxidants. In the present reaction Oxone

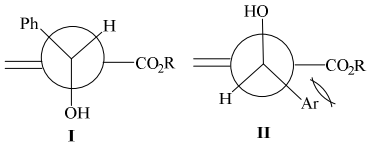
View Article Online
DOI: 10.1039/C7GC01483J

as the oxidant couples with inorganic halide salt (NaCl) to generate an active transient [Cl^+] species as shown in scheme 4. This undergoes electrophilic addition with MBH derived allylic alcohol **1a** on the electrophilic carbon centre from the sterically less hindered side to produce the intermediate **A**. This trigger the aryl migration and follows semipinacol type rearrangement to provide key chloro aldehyde **2a**.

As shown in transition state models, model **I** is more favoured. The steric effect of **II** is more due to proximity of Ar and –CO_2R as shown in Scheme 5. Having a sufficiently larger group like CO_2R is crucial for favourable attack of chloronium ion from the least hindered side and produces *anti*-isomer as major product.

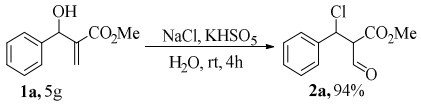


Scheme 4. Possible Reaction Mechanism



Scheme 5. Transition state models

To further demonstrate the synthetic expediency and industrial viability of this new methodology for scalability, a gram scale reaction was conducted using **1a** under standard reaction conditions to afford the desired product **2a** in 94% yield (Scheme 6).



Scheme 6. Gram-scale synthesis of **2a**

Conclusions

In summary, we have developed a mild, synthetically useful transformation of various MBH alcohols into corresponding β-chloro aldehydes. Notably the NaCl/Oxone system serves as an attractive alternative with oxone as oxidant and NaCl as Cl donar. Moreover, the method is safe, inexpensive, operationally simple and compatible with substrates bearing diverse functional groups. This represents an atom-economical and environmentally benign approach for construction of β-chloro aldehydes in aqueous conditions.

Acknowledgements

The authors are grateful to the financial assistance provided by CSIR-Senior Research Associateship (Scientist's Pool Scheme) and UGC-SRF Govt. of India, New Delhi. The authors acknowledge S. Sunder for providing the HRMS data. We also acknowledge Director IICT for providing infrastructural facilities.

Notes and references

1 (a) Bart I. Roman, Norbert De Kimpe, and Christian V. Stevens *Chem. Rev.*, 2010**, 110**, 5914; (b) A. M. R. Smith, K. K. Hii, *Chem. Rev.,* 2011, **111**, 1637.

2 (a) A. Butler and J. V.Walker, *Chem. Rev.,* 1993, **93**, 1937; (b) G. W. Gribble, *Chem. Soc. Rev.,* 1999, **28**, 335; (c) J. Ishida, H. Ohtsu, Y. Tachibana, Y. Nakanishi, K. F. Bastow, M. Nagai, H. K. Wang, H. Itokawab and K. H. Leeb, *Bioorg. Med. Chem.,* 2002, **10**, 3481.

3 A. Vigalok and A.W. Kaspi, *Top. Organomet. Chem.,* 2010, **31**, 19.

4 G. K. S. Prakash, T. Mathew, D. Hoole, P. M. Esteves, Q. Wang, G. Rasul and G. A. Olah, *J. Am. Chem. Soc.* 2004, **126**, 15770.

5 (a) A. Podgorsek and J. Iskra, *Molecules* 2010, **15**, 2857; (b) L. Gu, T. Lu, M. Zhang, L. Tou and Y. Zhanga, *Adv. Synth. Catal.,* 2013, **355**, 1077; (c) Y. Wang, Y. Wang, K. Jiang, Q. Zhang and D. Li, *Org. Biomol. Chem.*, 2016, **14**, 10180; (d) A. Podgorsek, M. Zupan and J. Iskra, *Angew. Chem. Int. Ed.*, 2009, **48**, 8424, and references cited therein.

6 (a) H. Hussain, I. R. Green and I. Ahmed, *Chem. Rev.,* 2013, **113**, 3329; (b) M. Eissen, M. Strudthoff, S. Backhaus, C. Eismann and G. Oetken, *J. Chem. Educ*., 2011, **88**, 284.

7 (a) J. Gao and G.-W. Wang, *J. Org. Chem.,* 2008, **73**, 2955; (b) B. Plietker, *Org. Lett.,* 2004, **6**, 289; (c) R. Singh, R. M. Kissling, M. A. Letellier and S. P. Nolan, *J. Org. Chem*., 2004, **69**, 209; (d) B. R. Travis, M. Sivakumar, G. O. Hollist and B. Borhan, *Org. Lett.,* 2003, **5**, 1031; (e) D. Yang and C. Zhang, *J. Org. Chem.,* 2001, **66**, 4814; (f) C. Bolm, A. S. Magnus and J. P. Hildebrand, *Org. Lett.,* 2000, **2**, 1173.

8 (a) S. Bhowmik and S. Batra, *Curr. Org. Chem.,* 2014, **18**, 3078; (b) T. Y. Liu, M. Xie and Y. C. Chen, *Chem. Soc. Rev*., 2012, **41**, 4101; (c) D. Basavaiah and G. Veeraraghavaiah, *Chem. Soc. Rev*., 2012, **41**, 68; (d) Y. Wei and M. Shi, *Acc. Chem. Res.,* 2010, **43**, 1005; (e) V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev*., 2009, **109**, 1; (f) V. Singh, S. Batra, *Tetrahedron* 2008, **64**, 4511; (g) D. K. Nair, S. M. Mobin and I. N. N. Namboothiri, *Org. Lett*., 2012, **14**, 4580; (h) B. Ressault, A. Jaunet, P. Geoffroy, S. Goudedranche and M. Miesch, *Org. Lett*., 2012, **14**, 366; (i) Y. L. Liu, B. L. Wang, J. J. Cao, L. Chen, Y. X. Zhang, C. Wang and J. Zhou, *J. Am. Chem. Soc.* 2010, **132** , 15176; (j) Y. L. Liu, X. Wang, Y. L. Zhao, F. Zhu, X. P. Zeng, L. Chen, C. H. Wang, X. L. Zhao and J. Zhou, *Angew. Chem. Int. Ed.*2013, **52**, 13735.

9 (a) J. W. Wilt and P. M. Aznavoorian, *J. Org. Chem.* 1978, **43**, 1285; (b) M. L. M. Pennings and D. N. Reinhoudt, *J. Org. Chem.* 1983, **48**, 4043; (c) A. Godard, P. Lamour, P. Ribereau, and G. Queguiner, *Tetrahedron* 1995, **51**, 3247; (d) N. De Kimpe, M. Boeykens, L. Lazar and G. Bernath, *Nat. Prod. Lett.* 1994, **5**, 1; (e) Jauch, J. *J. Prakt. Chem./Chem.Ztg.* 2000, **342**, 100.

10. Y. Jing, C. G. Daniliuc, and Armido Studer, *Org. Lett*., 2014, **16**, 4932.

11 (a) T. I. Temnikova and N. A. Oshueva, *Zh. Obshch. Khim.* 1963, **33**, 2464; (b) J. B. Christensen and A. Schluter, *Org. Prep. Proced. Int.* 1994, **26**, 355; (c) S. Uehira, Z. Han, H.

View Article Online
DOI: 10.1039/C7GC01483J

Shinokubo and K. Oshima, *Org. Lett.* 1999, **1**, 1383; (d) W. M. B. Konst, L. M. Vanderli and H. Boelens, *Tetrahedron Lett.* 1974, 3175; (e) O. G. Kulinkovich, V. L. Sorokin, A. Azzuz, S. V. Sviridov and N. V. Masalov, *Synthesis* 1993, 1059; (f) K. Griesbaum and G. Zwick, *Chem. Ber.* 1985, **118**, 3041.

12 M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati and A. Tsadjout, *Synlett* 2000, 813.

13 P. Sai Prathima, K. Srinivas and M. Mohan Rao *Green Chem.,* 2015, **17**, 2339.

14 (a) R. Schmidt, A. Stolle and B. Ondruschka, *Green Chem.,* 2012, **14**, 1673; (b) R. K. Dieter, L. E. Nice and S. E. Velu, *Tetrahedron Lett*., 1996, **37**, 2377.

15 (a) R. Bikshapathi, P. Sai Prathima, V. Jayathirtha Rao, *New J. Chem.,* 2016, **40**, 10300; (b) P. Sai Prathima, R. Bikshapathi, V. Jayathirtha Rao, *Tetrahedron Lett*, 2015, **56**, 6385; (c) R. Geesala, G. Jagadeesh Kumar, Gangasani, B. Mahender, B. Sridhar, V. Jayathirtha Rao, Amitava Das *Eur J Med Chem.,* 2016, **124**, 544.

16 B. Das, J. Banerjee and N. Ravindranath, *Tetrahedron* 2004, **60**, 8357.

17 (a) L. A. Paquette, D. R. Owen, R. T. Bibart, C. K. Seekamp, A. L. Kahane, J. C. Lanter and M. A. Corral, *J. Org. Chem*., 2001, **66**, 2828; (b) E. L. Ruggles and R. E. Jr. Maleczka, *Org. Lett*., 2002, **4**, 3899; (c) J. Li, Ch. L. Fu, G. F. Chen, G. B. Chai and S. M. Ma, *Adv. Synth. Catal.* 2008, **350**, 1376; (d) B. Alcaide, P. Almendros, A. Luna and M. R.Torres, *Adv. Synth. Catal.* 2010, **352**, 621; (e) B. M. Wang, Z. L. Song, C. A. Fan, Y. Q. Tu and W. M. Chen, *Synlett* 2003, **10**, 1497; (f) C. A. Fan, Y. Q. Tu, Z. L. Song, E. Zhang, L. Shi, M. Wang, B. M. Wang and S. Y. Zhang, *Org. Lett*. 2004, **6**, 4691.

18 (a) L. E. Overman, *Acc. Chem. Res*. 1992, **25**, 352; (b) L. E. Overman and L. D.Pennington, *J. Org. Chem*. 2003, **68**, 7143; (c) L. Kurti and B. Czako, *In Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, MA, 2005; pp 366.